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

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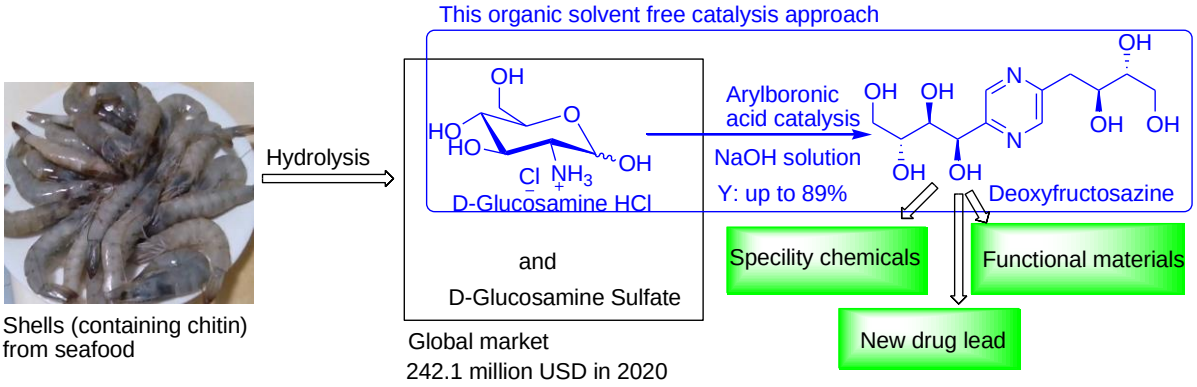
Abstract

Chitin is the most abundant N-containing polysaccharide in nature and D-glucosamine is one of the most successful commercial monomer products in the 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 a catalytic cycle of arylboronic acid via a boron transfer was also proposed.



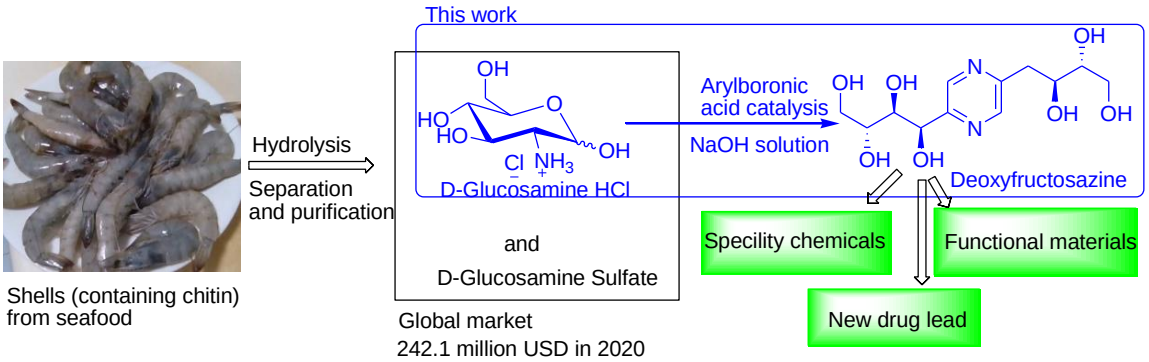
Key words: chitin; glucosamine; arylboronic acid catalysis; deoxyfructosazine; aqueous solution.

Introduction

Chitin is the second most abundant biopolymer in nature following cellulose, and the most abundant N-containing polysaccharide. Since only a few natural amines are available 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 the same from different sources, which led to more difficulty in followed modifications for derivatives.[3,4] Such recalcitrant structures usually lead to complex products in direct conversion of chitin into chemicals, and not surprisingly one of its hydrolysed

monomer N-acetyl-D-glucosamine (NAG) was frequently used for preparation of bio-based chemicals in uniform structure such as 3-acetamidofuran, 3-acetamido-5-acetylfuran (3A5AF), acetamidoacetaldehyde, pyridine and so on.[5] 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.[6] 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 a better nitrogen cycle. Here we report an arylboronic acids catalyzed dimerization of glucosamine forming deoxyfructosazine (**Scheme 1**); the reaction could be completed in a few hours and yield was excellent. Deoxyfructosazine is widely used in food industry,[7a] and it also showed antibacterial activity[7b]; Its therapeutic potential in treatments of diabetes[8], immunological diseases[9] and its DNA strand breakage activity[10] were also reported. its unique structure containing pyrazine moiety[11] and multiple hydroxyls[12] make it a very promising platform molecule for speciality chemicals and new smart materials.

Scheme 1. A "drop-in" change on current utilization of chitin via arylboronic acid catalysis.



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 dual solvent-catalyst[16a,b] or in deep eutectic solvents[16c] was also reported. However, yield of deoxyfructosazine was generally low to moderate either from self-condensation of D-glucosamine[13-16] or other monosaccharides with ammonia acid salts[17] even though more clues were achieved in mechanism investigation[16]. 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 progresses were 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] was 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 (0.1 M) 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 2 M HCl aqueous solution, and subsequently the mixture was stirred for another 30 mins. After that, 1 mL of the reaction mixture was taken out to another flask with ethanol for fast evaporation under reduced pressure at 33℃. Further drying in *vacuum* 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 bondings 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 (0.1 M, 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 2 M HCl aqueous solution, and subsequently the mixture was stirred for another 30 mins. After that, 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 *vacuum* 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 (0.1 M, 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 2 M 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 *vacuum* 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 a unique peak of DOF product at δ 5.20 and integration of a 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 neighbouring peaks (very small overlapped area in some entries). An analysis of sample spectra sees 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 (0.1 M, 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 2 M 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 *vacuum* 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 (0.05 mmol), 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).

1.6 General procedure of using maleic acid as an internal standard to calculate reaction yield (2 batches).

A) First batch: The reaction procedure was the same with that descripted in **1.5**. After reaction, removal of residual solvent in *vacuum* gave a crude product. Their weights: 170.5 mg with pyridine-4-boronic acid; 175.0 mg with 3-$NH_2C_6H_4B(OH)_2$; 157.7 mg with phenylboronic acid pinacol ester; 159.6 mg with $PhB(OH)_2$. The yield of DOF was quantitatively analyzed by ^{1}H NMR using maleic acid as an internal standard substance: the crude product was mixed with maleic acid (0.1 mmol, 11.6 mg), 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);

IntMa: Integration of alkene peak of maleic acid at δ 6.38 (2H);

Mol of DOF (2 × D-Glucosamine) = (IntDOF/IntMa) × 2 × 0.1 mmol;

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

$$\text{Yield}=2\times\frac{(\text{IntDOF/IntMa})\times 2\times 0.1\ \text{mmol}}{0.5\ \text{mmol}}\times 100\%$$

Yield: 83.2% with pyridine-4-boronic acid; 72.8% with 3-$NH_2C_6H_4B(OH)_2$; 75.2% with phenylboronic acid pinacol ester; 62.0% with $PhB(OH)_2$.

B) Second batch: The reaction procedure was the same with that descripted in **1.5**. After reaction, removal of residual solvent in *vacuum* gave a crude product. Their weights: 173.6 mg with pyridine-4-boronic acid; 177.6 mg with 3-$NH_2C_6H_4B(OH)_2$; 153.4 mg with phenylboronic acid pinacol ester; 161.7 mg with $PhB(OH)_2$. The yield of DOF was quantitatively analyzed

by ^{1}H NMR using maleic acid as an internal standard substance: a solution of maleic acid (0.5 mmol, 58.0 mg) and D_2O (5 mL) were prepared for use; the crude product was mixed with 1 mL of maleic acid solution (0.1 mmol/L), after mixing thoroughly, partial mixture was transferred to an NMR tube for ^{1}H NMR measurement.

Yield: 84.8% with pyridine-4-boronic acid; 75.2% with 3-$NH_2C_6H_4B(OH)_2$; 70.0% with phenylboronic acid pinacol ester; 59.2% with $PhB(OH)_2$.

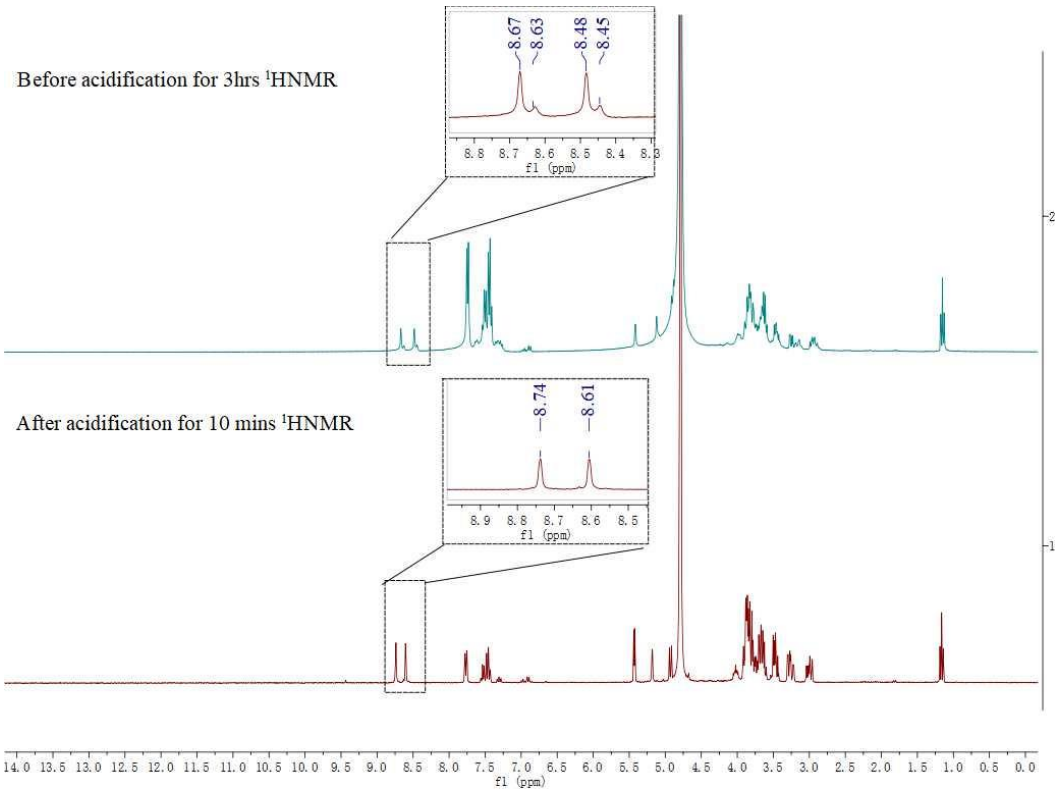
1.7 Procedure for quantitative ^{1}H NMR analysis for scale-up experiment (entry 11 in Table 3).

D-Glucosamine hydrogen chloride (2.0 g, 9.28 mmol) and 4-pyridyl$B(OH)_2$ (3.71 mmol) were added into a solution of NaOH (0.1 M, 121 mL), the mixture was stirred for 6 hours at 60℃ open to air. Then, one tenth of the reaction mixture (12.1 mL) was taken out and was acidified (pH value = 1-3) by dropwise addition of 2 M 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 *vacuum* gave a crude product (348 mg). The yield of DOF was quantitatively analyzed by ^{1}H NMR using maleic acid as an internal standard substance: the crude product was mixed with 2 mL of maleic acid solution (0.1 mmol/L in D_2O), after mixing thoroughly, partial mixture was transferred to an NMR tube for ^{1}H NMR measurement. Yield: 79.3%

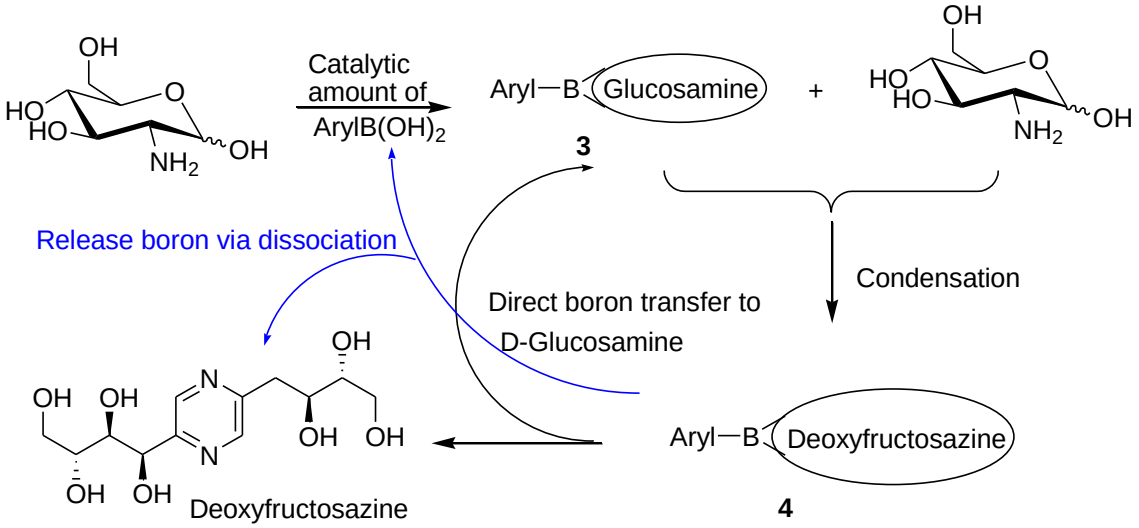
Results and discussion

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, 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 belonged to phenylboronic acid protected deoxyfructosazine. 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 the 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).



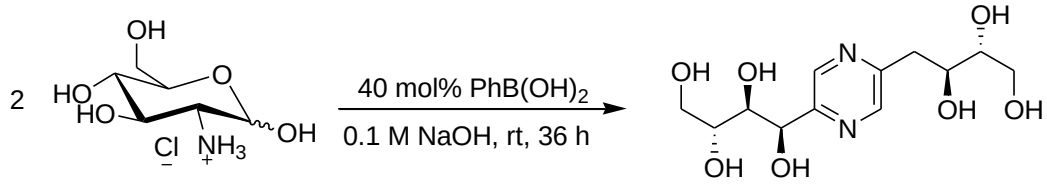
Scheme 2. Proposed catalytic cycle via boron transfer.



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 M 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

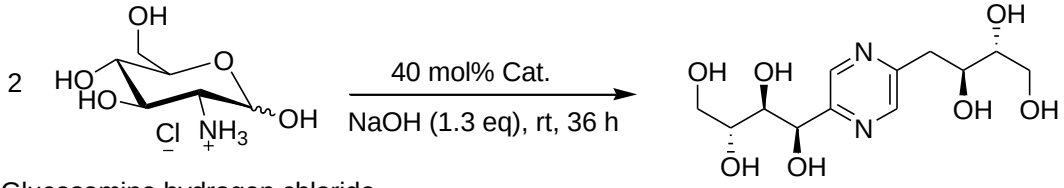
Deoxyfructosazine

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 M) 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 deoxyfructosazine and only a 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**) as well. 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 found that some electron-deficient groups had positive effect on reaction yield, but definitely electronic effect was not the only dominated factor. Subsequently some arylboronic acids with interactive groups on aromatic moiety were also evaluated (Entries 9 - 12, **Table 2**) in order to investigate the potential hydrogen bonding assistant effect. The existence of carboxylic acid group on 3-position or hydroxyl group on 4-position both led to lower yields of deoxyfructosazine (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 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	No catalyst	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 $ArB(OH)_2$ (0.2 mmol) were stirred in NaOH solution (6.5 mL; 0.1 M) for 36 h at room temperature.

[b] Determined by crude ^1H NMR.

[c] Contains trace fructosazine.

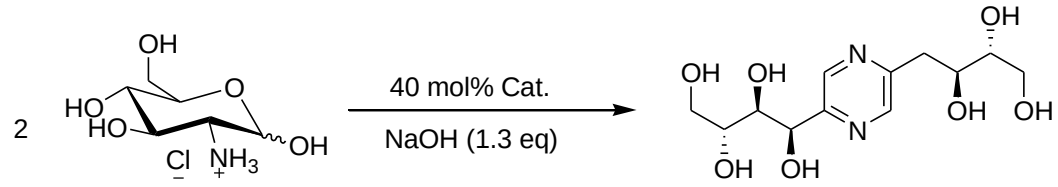
Since catalyst optimization indicated that 3-aminophenylboronic acid and 4-pyridylboronic acid showed better activity (Entries 11 and 12, **Table 2**), we further optimized reaction temperature in the presence of the two best catalysts as well as phenylboronic acid (**Table 3**). Initially a parallel study of self-condensation reactions with the three catalysts respectively (Entries 1 - 3, **Table 3**) was performed at 40℃ for 6 hours; and yields of deoxyfructosazine were comparable to these achieved at room temperature for 36 hours (Entries 1, 10 and 11, **Table 2**). Optimization of catalyst loading of $PhB(OH)_2$ at 40℃ were also carried out for 6 hours (STable 1 in supporting information). In the absence of catalyst, no deoxyfrutosazine or fructosazine was achieved, and raw material D-glucosamine was still observable along with some beta-form. With 10 mol% catalyst, both deoxyfrutosazine and fructosazine formed in a low yield; meanwhile increase of catalyst loading to 20 mol% led to a clean conversion with a sole product of deoxyfrutosazine in 46% yield. Yields of 52% and 62% were obtained respectively in the presence of 30 mol% and 40 mol% catalyst.

Prolonged reaction time to 12 hours only slightly improved yields for all reactions with the 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 product from decomposition of D-glucosamine was observed. A possible reason for remarkable increase of reaction yield is that aggregation of D-glucosamines boronic ester and subsequent boron transfer from DOF to D-glucosamine are both accelerated, leading to a higher turnover of arylboronic acid catalyst

at higher temperature. Even though 4-pyridylboronic acid catalyst still showed the highest activity (Y: 89%), yield difference with either of 3-aminophenylboronic acid (Y: 86%) and phenylboronic acid (Y: 85%) became very narrow. A further optimization on base use at 40℃ or 60℃ with 40 mol% $PhB(OH)_2$ or 40 mol% $3\text{-}NH_2C_6H_4B(OH)_2$ as a catalyst showed similar trend with previous optimization at room temperature (detail sees **STable 2** in supporting information). Via boron transfer, phenylboronic acid pinacol ester could also catalyze the self-condensation and the yield was comparable with that with $PhB(OH)_2$ (Entry 10, **Table 3**).

Because yields of deoxyfructosazine were all measured by crude ^1H NMR without internal standard, another three repeated reactions were carried out and their crude products were measured with pyrazine or maleic acid as an 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 ^1H NMR Spectra in experimental section). The average yield of repeated reaction in entry 7 with either of two internal reagents was 65% (Y: 85% without internal reagent); the average yield of two repeated reactions in entry 8 with maleic acid as an internal reagent was 74% (Y: 86% without internal reagent); the average yield of three repeated reactions in entry 9 with either of two different internal reagents was 86% (Y: 89% without internal reagent). The small difference between yield measured w/o an internal standard and that with an internal standard for these two cases indicated that the data obtained in the absence of an internal standard is acceptable in accuracy for this particular condensation reaction. A scale-up (D-glucosamine HCl, 2 grams) with the best arylboronic acid catalyst (40 mol%) was also performed open to air and yield with maleic acid as an internal standard was 79% (Entry 11, **Table 3**). The excellent yields obtained under optimized conditions indicated this catalytic condensation in the presence of arylboronic acids is 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	$3\text{-}NH_2C_6H_4$	40℃	6	69
3	4-Pyridyl	40℃	6	74
4	Phenyl	40℃	12	69
5	$3\text{-}NH_2C_6H_4$	40℃	12	70
6	4-Pyridyl	40℃	12	78
7	Phenyl	60℃	6	85 (65[b])
8	$3\text{-}NH_2C_6H_4$	60℃	6	86 (74[b])
9	4-Pyridyl	60℃	6	89 (86[b])
10	Phenyl (pinacol ester)	60℃	6	73[b]
11	4-Pyridyl[c]	60℃	6	79[b]

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

[b] Determined by average crude ^{1}H NMR with internal reagent;

[c] 2 grams of D-glucosamine HCl was used.

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 acid catalysis in water for upgrade of D-glucosamine for deoxyfructosazine very attractive. Although no online data is available for the annul market size of deoxyfructosazine, we estimated the 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 studies and experimental data of complex of D-glucosamine-arylboronic acid is not yet known to our best of knowledge. Mechanistic understanding on how arylboronic acid interacts with D-glucosamine and subsequently interacts with condensation product deoxyfructosazine as well as dissociation/transfer from deoxyfructosazine would be of much importance to future design of more efficient arylboronic acid catalystic system.

For the 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 studies focused on boric acid, but it is well known that arylboronic acids and boric acids 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 one 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 an important role in perturbing the hydrogen bonding network of monosaccharides and bulk water. In this study we also observed obvious shifts on crude ^{1}H NMR spectra from control reaction with only D-glucosamine hydrogen chloride in NaOH solution (Entry 1, **Table 2**). Meanwhile, a much bigger peak at δ 4.96 (proton of anomer

position for beta-form) in the absence of arylboronic acid 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 experiments 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 were 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 $(PhB)_2(\beta\text{-D-Arap}H_4)$[35] prepared with D-arabinose in the presence of two equivalents of phenylboronic acid. Very recently a 1:1 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 protons at the anomer position overlapped with the big water peak, a chelation at 3,4-*cis* position is more probable because two *cis*-hydroxyls are more favorable to form ester bonds[30,35] with phenylboronic acid. In both 3,4-*cis* chelated arylboronic ester, participation of hydroxyl group at C_6 position forming ternary boronate complexes was also possible even though no evidence is available at this moment.

Interaction of arylboronic acid and deoxyfructosazine

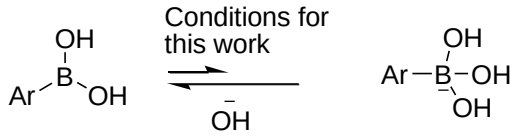
Although three types of borate esters (1,2-bidentate, tridentate and 1,2-bidentate with interaction to nitrogen) were detected in solution of disodium tetraborate (excess)/glucosamine hydrogen chloride via ^{11}B/^{13}C NMR spectroscopy[13] in reported literature, in our study majority of deoxyfructosazine was in free form and only a 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 system, 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 conditions, 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 from 8.35 to 8.21 at 30 mins, values ranging from 8.07 to 8.00 at 3 hours and values ranging from 8.06 – to 7.97 at 12 hours were obtained, and the results indicated reactions proceeded in alkaline solution (**Scheme 3**). According to pioneering mechanistic study between arylboronic acids and diols in aqueous solution by K. Ishihara[37], in alkaline solution order of

kinetic reactivities of boronic species 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

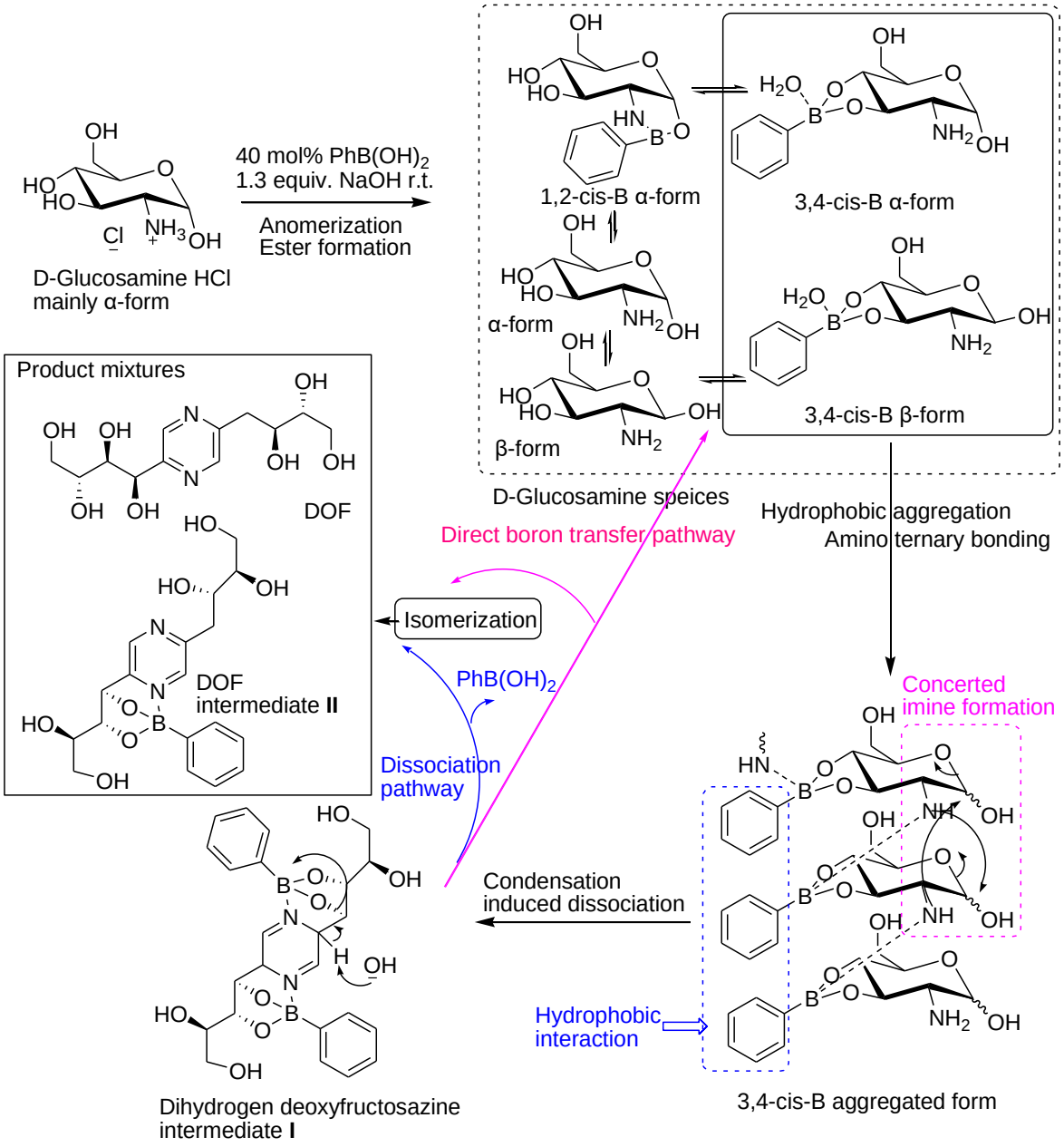
Proposed boron transfer mechanism

With clues in hand, here we proposed an arylboronic acid catalysis mechanism (**Scheme 4**) in which pH enabled boron transfer is a key step for a catalytic cycle. Initially moderate water-soluble arylboronic acid (solubility in water: 10 g/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 like surfactants because of hydrophobic nature of aryl moieties, and they tend to aggregate due to hydrophobic effect and potential aromatic π-π interaction;[39] ternary complexes might likely also form via coordinating to amino functional group of another glucosamine and such intermolecular coordination was known in literature[40]. Such hydrophobic aggregation might explain the accelerated rate of condensation in aqueous solution by arylboronic acid. similar hydrophobic interaction was proposed to explain the drastic acceleration of Diels-Alder reaction and benzoin condensation in aqueous media.[39] However, whether such hydrophobic interactions lead to micelles[41] in our system is still unknown and to be answered in future mechanistic study.

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 narrower when temperature was increased to 60°C (hydrogen bonding would be much weaker at high temperature). Such aggregated 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) in a concerted manner because the aldehyde peak from acyclic form of glucosamine was never observed in all ^1H NMR tracking experiments (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 if 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 and better water solubility. A subsequent chem-selective dehydration directed by arylboronic ester[42] 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; Reaction with phenylboronic acid pinacol ester (Entry 10, **Table 3**) gave a comparable yield of DOF to reaction with the same amount of phenylboronic acid, also indicating the presence of fast boron transfer in the system. 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 a new glucosamine 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).

Scheme 4. Proposed boron transfer mechanism.



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 a new drug lead and design of specialty chemicals/functional materials in the future because of its unique structure containing pyrazine moiety and multiple hydroxyls. Regarding broad use of high-end specialty 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 specialty chemicals/functional materials looks more practical in the near future toward decarbonation in chemical industry.

Mechanistic studies 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 step for the catalysis cycle. Such new insights might be of much importance for further improvement of this condensation process and design of new arylboronic acids for catalyzing selective monosaccharides transformations in aqueous media.

Supporting Information

Two STables on optimization of catalyst loading and use of NaOH, STable 3 on a comparison of this work with reported methods, general procedures for all tables in manuscript and STables as well as calculation of ^{1}H NMR yields with two different internal standards, all ^{1}H NMR spectra are available in the Supporting Information.

Declaration of Interests

The authors declare that they have no known competing financial interests.

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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Reference

[1] Froidevaux, V.; Negrell, C.; Caillol, S.; Pascault, J.-P. and Boutevin, B. Biobased Amines: From Synthesis to Polymers; Present and Future *Chem. Rev.* **2016**, *116*, 14181–14224.

[2] Shi, X.; Ye, X.; Zhong, H.; Wang, T.; Jin, F. Sustainable nitrogen-containing chemicals and materials from natural marine resources chitin and microalgae. *Mol.* **2021**, *505*, 111517.

[3] Joseph, S. M.; Krishnamoorthy, S.; Paranthaman, R.; Moses, J. A.; Anandharamakrishnan C. A review on source-specific chemistry, functionality, and applications of chitin and chitosan. *Carbohydrate Polymer Technologies and Applications* **2021**, *2*, 100036.

[4] Berezina, N. Production and application of chitin. *Phys. Sci. Rev*. **2016**, 20160048.

[5] Chen, X.; Yang, H.; and Yan, N. Shell Biorefinery: Dream or Reality? *Chem. Eur. J.* **2016**, *22*, 13402-13421.

[6] Xie, S.; Jia, C.; Ong, S. S. G.; Wang, Z.; Zhu, M.; Wang, Q.; Yang, Y.; and Lin H. A Shortcut Route to Close Nitrogen Cycle: Bio-Based Amines Production via Selective Deoxygenation of Chitin Monomers over Ru/C in Acidic Solutions. *iScience* **2020**, *23*, 101096.

[7] a) Soladoye, O. P.; Pietrasik, Z.; Hrynets, Y.; Betti, M. The effect of glucosamine and glucosamine caramel on quality and consumer acceptability of regular and reduced salt breakfast sausages, *Meat Sci.*, **2021**, *172*, 108310; b) Hrynets, Y.; Bhattacherjee, A.; Ndagijimana, M.; Martinez, D. J. H. and Betti, M. Iron (Fe^{2+})-Catalyzed Glucosamine Browning at 50°C: Identification and Quantification of Major Flavor Compounds for Antibacterial Activity. *J. of Agric. and Food Chem.* **2016,** *64*, 3266-3275.

[8] Evers, M. Association of deoxyfructosazine and an antidiabetic of the biguanide family WIPO (PCT) patent: wo2001047522A3, **2002**.

[9] Zhu, A.; Huang, J.; Clark, A.; Romero, R.; Petty, H. R. 2,5-Deoxyfructosazine, a D-glucosamine derivative, inhibits T-cell interleukin-2 production better than d-glucosamine. *Carbohydr. Res.*, **2007**, *342*, 2745-2749.

[10] Sumoto, K.; Irie, M.; Mibu, N.; Miyano, S.; Nakashima, Y.; Watanabe, K.; Yamaguchi, T. Formation of Pyrazine Derivatives from D-glucosamine and Their Deoxyribonucleic acid (DNA) Strand Breakage Activity. *Chem. Pharm. Bull.,* **1991**, *39*, 792.

[11] Scutelnic, V.; Tsuru, S.; Pápai, M.; Yang, Z.; Epshtein, M.; Xue, T.; Haugen, E.; Kobayashi, Y.; Krylov, A. I.; Møller, K. B.; Coriani, S. & Leone, S. R. X-ray transient absorption reveals the Au ($n\pi^*$) state of pyrazine in electronic relaxation. *Nat. Commun.* **2021**, *12*, 5003.

[12] H. Sardon, D. Mecerreyes, A. Basterretxea, L. Avérous, and C. Jehanno From Lab to Market: Current Strategies for the Production of Biobased Polyols. *ACS Sustainable Chemistry & Engineering* **2021** *9*, 10664-10677.

[13] Rohovec, J.; Kotek, J.; Peters, J. A. and Maschmeyer, T. A Clean Conversion of D‐Glucosamine Hydrochloride to a Pyrazine in the Presence of Phenylboronate or Borate. *Eur. J. Org. Chem.*, **2001**, 3899-3901.

[14] Kuhn, R.; Kruger, G.; Haas, H. J.; Seeliger, A. Aminozucker‐Synthesen, XXIV. Pyrazinbildung aus Aminozuckern. *Justus Liebigs Ann. Chem.*, **1961**, *644*, 122-127.

[15] Pan, H. Recent Progress in Organic Transformations Catalyzed by Organoboronic Acids. *China Petroleum and Chemical Standard and Quality,* **2013**, *12*, 34, in Chinese.

[16] a) Jia, L.; Zhang, Z.; Qiao, Y.; Pedersen, C. M.; Ge, H.; Wei, Z.; Deng, T.; Ren, J.; Liu, X.; Wang, Y. and Hou, X Product Distribution Control for Glucosamine Condensation: Nuclear Magnetic Resonance (NMR) Investigation Substantiated by Density Functional Calculations. *Ind. Eng. Chem. Res*., **2017**, *56*, 2925-2934; b) Jia, L.; Wang, Y.; Qiao, Y.; Qi, Y. and Hou, X. Efficient one-pot synthesis of deoxyfructosazine and fructosazine from d-glucosamine hydrochloride using a basic ionic liquid as a dual solvent-catalyst *RSC Adv.*, **2014**, *4*, 44253-44260; c) Wu, M.; Ma, H.; Ma, Z.; Jin, Y.; Chen, C.; Guo, X.; Qiao, Y.; Pedersen, C. M.; Hou, X. and Wang, Y. Deep Eutectic Solvents: Green Solvents and Catalysts for the Preparation of Pyrazine Derivatives by Self-Condensation of d-Glucosamine. *ACS Sustainable Chemistry & Engineering* **2018**, *6*, 9434-9441.

[17] a) H. Tsuchida, M. Komoto, H. Kato, M. Fujimaki, Formation of Deoxy-fructosazine and Its 6-Isomer on the Browning Reaction between Glucose and Ammonia in Weak Acidic Medium. *Agric. Biol. Chem.*, **1973**, *37*, 2571–2578; b) S. Filonenko, A. Voelkel and M. Antonietti Valorization of monosaccharides towards fructopyrazines in a new sustainable and efficient eutectic medium. *Green Chem.,* **2019**, *21*, 5256-5266.
[18] Boronic Acids—Preparation and Applications in Organic Synthesis Medicine and Materials (Ed.: D. G. Hall), 2nd Ed., Wiley-VCH, Weinheim, **2011**.

[19] Zheng, H.; Ghanbari, S.; Nakamura, S. and Hall, D. G. Boronic Acid Catalysis as a Mild and Versatile Strategy for Direct Carbo- and Heterocyclizations of Free Allylic Alcohols. *Angew. Chem. Int. Ed.* **2012**, *51*, 6187-6190.

[20] Boronic Acid-catalyzed Reactions of Carboxylic Acids (K. Ishihara), part of "Synthesis and Application of Organoboron Compounds" (Ed: E. Fernandez, A. Whiting), Springer, **2015**, pp243-270.

[21] Nishi, N.; Nashida, J.; Kaji, E.; Takahashi, D.; Toshima, K. Regio- and Stereoselective β-Mannosylation using a Boronic Acid Catalyst and Its Application in the Synthesis of a Tetrasaccharide Repeating Unit of Lipopolysaccharide Derived from *E. coli* O75. *Chem. Commun*., **2017**, *53*, 3018-3021.

[22] Tanaka, M.; Nakagawa, A.; Nishi, N.; Iijima, K.; Sawa, R.; Takahashi, D.; Toshima, K. Boronic-Acid-Catalyzed Regioselective and 1,2-cis-Stereoselective Glycosylation of Unprotected Sugar Acceptors via SNi-Type Mechanism. *J. Am. Chem. Soc.* **2018**, *140*, 3644-3651.

[23] Kuwano, S.; Hosaka, Y. and Arai, T. Chiral Benzazaborole-Catalyzed Regioselective Sulfonylation of Unprotected Carbohydrate Derivatives *Chem. Eur. J.* **2019**, *25*, 12920-12923.

[24] Dailler, D.; Dorst, A.; Schäfle, D.; Sanderet, P.& Gademannal, K. Novel fidaxomicin antibiotics through site-selective catalysis. *Commun Chem.* **2021**, *4*, 59.

[25] Gu, L.; Lim, J.; Cheong, J. L. and Lee, S. S. MCF-supported Boronic Acids as Efficient Catalysts for Direct AmideCondensation of Carboxylic Acids and Amines. *Chem. Commun.* **2014**, *50*, 7017-7019.

[26] The solvent peak between 1.0 ppm to 1.25ppm belonged to residual ethanol because ethanol was added for fast evaporation of water solvent after acidification of completed reactions (detail see supporting information).

[27] Data from www.ktvn.com: Glucosamine Market Size is Estimated to Grow with a CAGR of 1.5% - KTVN Channel 2 - Reno Tahoe Sparks News, Weather, Video.

[28] Springsteen, G. and Wang, B. A Detailed Examination of Boronic acid–diol Complexation. *Tetrahedron*, **2002**, *58*, 5291-5300.

[29] Ni, N.; Laughlin, S.; Wang, Y.; Feng, Y.; Zheng, Y.; Wang, B. Probing the General Time Scale Question of Boronic Acid Binding with Sugars in Aqueous Solution at Physiological pH. *Bioorg. Med. Chem.*, **2012**, *20*, 2957-2961.

[30] Peters, J. A. Interactions between boric acid derivatives and saccharides in aqueous media: Structures and stabilities of resulting esters *Coord. Chem. Rev.* **2014**, *268*, 1–22.

[31] Kurogochi, M.Mizuno, M. Matsuda, A. Binding Assessment of Monosaccharide–Boronic Acid Complexes via Tandem Mass Spectrometry. *ChemistrySelect* **2018**, *3*, 8193-8198.

[32] Jia, L.; Liu, X.; Qiao, Y.; Pedersen, C. M.; Zhang, Z.; Ge, H.; Wei, Z.; Chen, Y.; Wen, X.; Hou, X.; Wang, Y. Mechanism of the self-condensation of GlcNH2: insights from in situ NMR spectroscopy and DFT study, *Applied Catalysis B: Environmental* **2017**, *202*, 420-429.

[33] Barker, S. A.; Chopra, A. K.; Hatt, B. W. and Somers, P. J. The interaction of areneboronic acids with monosaccharides. *Carbohydr. Res.* **1973**, *26*, 33-40.

[34] Zhu, G.; Li, H.; Li, Y.; Gu, L. "NMR Elucidation of Observed Stable Sugar-NaCl-water Complexes in Aqueous Solution" preprint at *ChemRxiv* (2021). Link: 10.33774/chemrxiv-2021-t8k0j-v2. (Submitted and under review).
[35] Reichvilser, M. M.; Heinzl, C.; Klüfers, P. Boronic acid mono- and diesters of the aldopentoses, *Carbohydr. Res.*, **2010**, *345*, 498-502.
[36] Jia, L.; Liu, R.; Lv, J.; Liu, L.; Zhang, Z.; Wang, Y. and Hou, X. Probing the interactions of $GlcNH_2$ with boric acid *via* NMR spectroscopy. *Phys. Chem. Chem. Phys.*, **2021**, *23*, 15758-15765.
[37] Furikado, Y.; Nagahata, T.; Okamoto, T.; Sugaya, T.; Iwatsuki, S.; Inamo, M.; Takagi, H. D.; Odani, A.; Ishihara, K. Universal Reaction Mechanism of Boronic Acids with Diols in Aqueous Solution: Kinetics and the Basic Concept of a Conditional Formation Constant. *Chem. Eur. J.,* **2014**, *20*, 13194-13202.

[38] Khokhlova, E.A.; Kachala, V. V.; Ananikov, V. P. The first molecular level monitoring of carbohydrate conversion to 5-hydroxymethylfurfural in ionic liquids. B_2O_3--an efficient dual-function metal-free promoter for environmentally benign applications. *ChemSusChem*, **2012**, *5*, 783-789.
[39] R. Breslow Hydrophobic effects on simple organic reactions in water. *Acc. Chem. Res.,* **1991**, *24*, 159-164.

[40] Bosch, L. I.; Fyles, T. M.; James, T. D. Binary and ternary phenylboronic acid complexes with saccharides and Lewis bases. *Tetrahedron*, **2004**, *60*, 11175-11190.

[41] J. B. F. N. Engberts and M. J. Blandamer Understanding organic reactions in water: from hydrophobic encounters to surfactant aggregates. *Chem. Commun.*, **2001**, 1701-1708.

[42] Istasse, T.; Lemaur, V.; Debroux, G.; Bockstal, L.; Lazzaroni, R.; Richel, A. Monosaccharides Dehydration Assisted by Formation of Borate Esters of α-Hydroxyacids in Choline Chloride-Based Low Melting Mixtures. *Front. Chem.*, **2020**, *8*: 569.