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# Integration of Enzymatic and Heterogeneous Catalysis for One-pot Production of Fructose from Glucose

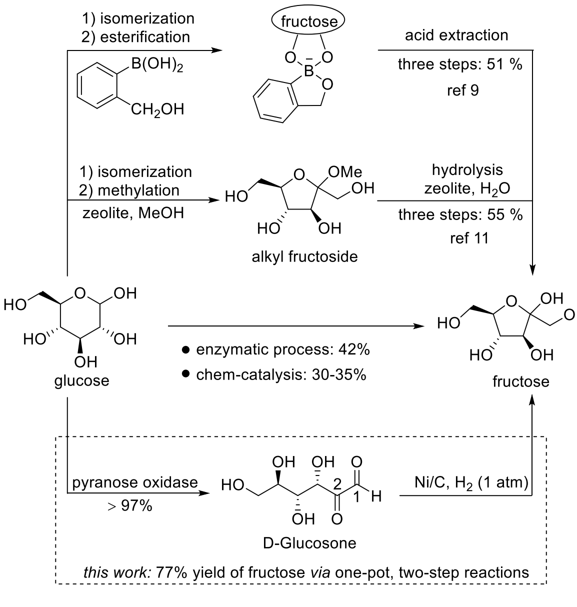
Jiankui Sun,[a] Helong Li,[a] Hongzhi Huang,[b] Bo Wang,[a] Ling-Ping Xiao[a] and Guoyong Song*[a]

**Abstract:** The search for efficient routes for the production of fructose from biomass-derived glucose is of great interest and importance as fructose is a highly attractive substrate in the conversion of cellulosic biomass to biofuels and chemicals. We herein report a one-pot, multi-step procedure involving enzyme-catalyzed oxidation of glucose at C2 position and Ni/C-catalyzed hydrogenation of D-glucosone at C1 position selectively, thus giving a remarkable 77% yield of fructose. Starting from upstream substrates such as *α*-cellulose and starch, fructose was also generated with similar efficiency and selectivity by the combination of enzymatic and heterogeneous catalysis. This method constitutes a new protocol for preparation of fructose from biomass-derived substrates in an efficient fashion.

Fructose is widely used in the food industry, which contributes many useful physical and functional attributes to food and beverage applications.[1] In addition, recent investigations on conversion of biomass to biofuels and fine chemicals confirmed that fructose is a superior substrate compared to glucose.[2,3] Currently, the isomerization of glucose to fructose for production of high-fructose corn syrups (HFCS) has become the largest immobilized biocatalytic manufacturing process worldwide, reaching a global production as 8.5 million tons in 2015.[4] The industrial isomerization of glucose to fructose is performed in aqueous phase by using an immobilized enzyme (xylose isomerase), which usually gives a mixture of 42% fructose, 50% glucose and 8% other saccharides, because this isomerization reaction is governed by thermodynamic equilibrium ($K_{eq} \approx 1$ at 298 K) (Scheme 1).[5] This entails the problem that enriching or isolation of fructose from the reaction mixture needs the use of elaborate and costly preparative column chromatography.[1]

As an alternative to enzyme catalysis, glucose can also be isomerized to fructose in the presence of a chemical catalyst.[5d,6-8] Despite significant efforts have been devoted to designing efficient chemical catalysts, including Lewis acid[6,7] and Brønsted base[8] catalysts, the fructose yields were limited to 30–35% (Scheme 1), being inferior to enzymatic catalysts. Recently, *in situ* complexation of fructose with borates,[9] aluminates[10] or methanol[11] was reported as a new method to improve the fructose yield in chemical catalysis, wherein the concentration of fructose in the isomerization reaction mixture decreased and the glucose–fructose equilibrium shifted towards fructose. In 2013, Riisager and coworkers reported a zeolite-catalyzed multi-step reaction route involving isomerization, methylation and hydrolysis, which gave 55% yield of fructose finally (Scheme 1).[11] In 2016, Palkovits used (2-(hydroxymethyl)phenyl)boronic acid (HMPBA) to covalently bond fructose in a $Na_2HPO_4/NaH_2PO_4$ catalytic system, leading to formation of fructose-HMPBA complexes, which can release fructose up to 51% yield after acid extraction (Scheme 1).[9]

The integration of heterogeneous chemical and biological catalysis has been regarded as an important strategy for producing chemicals from biomass, especially in cascade-type redox reactions.[12] For example, Froidevaux, Delcroix and Dumeignil proposed that sorbitol generated from hydrogenation of glucose by a chemcatalyst, can be oxidized into fructose in the presence of a sorbitol dehydrogenase.[12g] It is well known that glucose can be oxidized at C2 position with pyranose oxidases[13] (or immobilized enzyme)[13b,14], leading to formation of dicarbonyl D-glucosone, an important precursor for biosynthesis of the antibiotic cortalcerone. Theoretically, it is possible that D-glucosone can be hydrogenated into fructose selectively at C1 position (aldehyde unit). Two patents have confirmed such process by using a palladium catalyst[14] or xylose reductase,[15] thus providing a new pathway to generate a high yield of fructose by overcoming reaction equilibrium between glucose and fructose.[12a] However, these two-step reactions suffer from costly Pd or reductase catalyst and complicated intermediate isolation. Alternatively，the low-cost metal catalyst, such as Raney Ni, was also used for hydrogenation of D-glucosone, which afforded fructose in a low



**Scheme 1**. General procedures for preparation of fructose from glucose

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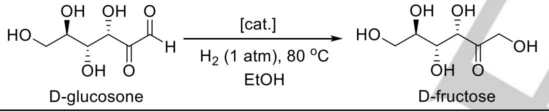
yield (30%) because of further hydrogenation of fructose.[14] Herein, we reported a two-step procedure for synthesis of fructose from glucose in a high yield, involving pyranose oxidase-catalyzed oxidation of fructose at C2 position and Ni/C-catalyzed hydrogenation of D-glucosone at C1 position. The enzymatic and heterogeneous catalysis can be integrated into one-pot procedure without any intermediate purification.

The first oxidative reaction step for the approaches shown in Scheme 1 was carried out under citric acid butter (pH = 5) in air at 30 °C, in which all of the enzymes were quite active. The glucose 2-oxidase (*EC 1.1.3.10*, 620 U, 2 wt%), isolated from *Trametes hirsute*, can efficient catalyze D-glucose (5% w/v) into D-glucosone *via* selective C2 oxidation quantitatively in 24 h, whereas oxygen acted as an oxidant and a catalase (2 wt%) was used to convert $H_2O_2$. This reaction in $O_2$ atmosphere is faster than in air.[13e]

After successful achieving enzyme-catalyzed oxidation of glucose, we then investigated the hydrogenation of D-glucosone in the presence of a series of heterogeneous transition metal catalysts including nickel, palladium, ruthenium and platinum. On the treatment of D-glucosone with Ni/C (Ni content: 5 wt%, 1:15 Ni:D-glucosone molar ratio) and 1 atm $H_2$ at 80 °C in EtOH for 12 h, a complete conversion of D-glucosone was observed, which gave a mixture of D-fructose (65.2%) *via* hydrogenation aldehyde moiety (C1), D-glucose (17.2%) *via* hydrogenation ketone moiety (C2), D-mannitol (12.6%) and D-sorbitol (3.6%) *via* dual hydrogenation (Table 1, entry 1). A trace of D-mannose (*ca*. 0.5%) was also detected in the mixture, which can be to hydrogenate into mannitol rapidly.[16] Ethyl fructoside, possibly generated from the reaction of D-fructose with EtOH,[17] was not observed under current reaction conditions (SI). Nickel supported on amorphous-silica-alumina (Ni/ASA)[18] also showed a high activity, but gave a slight lower fructose yield (63%) under similar reaction conditions (Table 1, entry 2). The precious metal catalysts, such as Pd/C, Ru/C and Pt/C, were slight more selective than Ni catalysts, gave D-fructose in 65.8–67.6% yields in 9 h (Table 1, entries 3-5). Decreasing the dosage of Ni/C (Ni content: 5 wt%) to 25 wt% (where molar ratio of Ni : D-glucosone is 1:27) or employing a low Ni loading catalyst (Ni content: 2 wt%, molar ratio of Ni : D-glucosone is 1:17) resulted in a drop in activity, while the products distributions and selectivity to fructose (62.6% and 62.1%, respectively) remain unchanged (Table 1, entries 7-8). These yields compare well with reports of fructose synthesis from glucose through isomerization reaction using xylose isomerase[19] and chemical catalysts.[7a] Taking account of the cost of catalyst, Ni/C was chosen for subsequent investigation.

**Table 1.** Hydrogenation D-glucosone over various catalysts[a]



| entry | catalyst | time (h) | Con. (%) | yields (mol %)[b] | | | |
|---|---|---|---|---|---|---|---|
| | | | | fructose | glucose | mannitol | sorbitol |
| 1 | Ni/C | 12 | 100 | 65.2 | 17.2 | 12.6 | 3.6 |
| 2 | Ni/ASA | 12 | 100 | 63.0 | 18.1 | 13.5 | 4.6 |
| 3 | Pd/C | 9 | 100 | 66.8 | 17.1 | 12.6 | 2.8 |
| 4 | Ru/C | 9 | 100 | 67.6 | 16.5 | 12.3 | 2.6 |
| 5 | Pt/C | 9 | 100 | 65.8 | 17.3 | 13.1 | 2.9 |
| 6 | Ni/C[c] | 24 | 94.6 | 60.3 | 15.9 | 13.6 | 4.3 |
| 7 | Ni/C[d] | 48 | 92.1 | 57.6 | 15.6 | 14.1 | 4.1 |
| 8 | Ni/C[e] | 48 | 90.3 | 56.1 | 15.7 | 14.0 | 4.1 |

[a] Reaction conditions: D-glucosone (0.28 mmol, 50 mg), catalyst (50 mg), EtOH (5 mL), $H_2$ (1 atm); The metal content in catalysts is 5 wt % in entries 1-7. D-fructose exists in different conformations which vary with the polarity of the reaction medium and the open-chain form is depicted here. [b] Determined by HPLC and ion chromatography by comparison with authentic samples. [c] 25 mg 5 wt % Ni/C was used. [d] 13 mg 5 wt % Ni/C was used. [e] 50 mg 2 wt % Ni/C was used.

A range of solvents were screened in the hydrogenation of D-glucosone with Ni/C under $H_2$ atmosphere and the results are summarized in Figure 1 and Table S1. The hydrogenation reactions in MeOH, $^i$PrOH and $H_2O$ proceeded to give complete conversions of D-glucosone in 12 h at 80 °C with Ni/C. It looks that the selectivity towards D-fructose increased with the solvent polarity.[20] For example, water having a high $E_T(30)$[20] value (63.1 kcal mol$^{-1}$) enabled high selectivity to D-fructose (67.5%) and D-glucose (20%), wherein the yield of D-mannitol decreased to 6.2%, probably because the formation of D-mannose was suppressed in water.[6c,21] EtOH ($E_T(30)$ = 51.9 kcal mol$^{-1}$) gave D-fructose in 65.2% yield, in which low yields of D-glucose (17.2%) and sorbitol (3.6%) were observed. In the case of $^i$PrOH with $E_T(30)$ value as 48.4 kcal mol$^{-1}$, a significant drop of D-fructose (58.7%) and a raise of D-mannitol (12.3%) were observed. Therefore, we focused on the study of binary solvent mixture of EtOH and $H_2O$. Further screening indicated that the mixed EtOH/$H_2O$ in 7: 1 (v/v) as the best choice,[22] in which fructose yield was improved to 78.5%, together with the formation of glucose (13.2%), mannitol (6.7%) and sorbitol (1.1%) as byproducts.

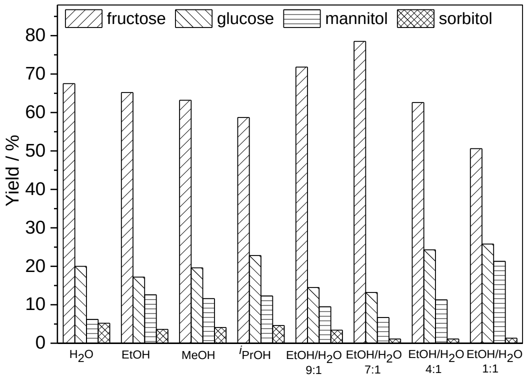


**Figure 1**. Influences of solvents of Ni/C-catalyzed hydrogenation of D-glucosone

The hydrogenation reaction of D-glucosone was further carried out over Ni/C at different reaction temperature in EtOH/$H_2O$ (7: 1) under 1 atm $H_2$ atmosphere, and the results were summarized in Figure 2 and Table S3. In the case of a low reaction temperature, a drop in activity was observed as seen in the case of 50 $^oC$ (19.2% conversion, 24 h) and 70 $^oC$ (90.1% conversion, 20 h), while the selectivity towards D-fructose remained high (71.4% and 76.2%, respectively). Increasing the temperature to 100 $^oC$ led to an obvious decreased fructose yield (41.5%), together with the observation of increasing of D-mannitol (32.8%) and D-sorbitol (10.3%). The influence of $H_2$ pressure in the range of 1−20 atm was also investigated. As shown in Figure 3 and Table S2, the distribution of D-fructose was decreased obviously, while the yields of D-glucose, D-mannitol and D-sorbitol were increased under high $H_2$ pressure. Hydrogenation of D-glucosone at C2 position (ketone unit) leading to the formation of D-glucose probably features higher energy profile than the formation of D-fructose at C1 position due to steric hindrance. Therefore, the high $H_2$ pressure and/or high temperature are favorable for generation D-glucose and other byprodcts through further hydrogenation. In the absence of $H_2$, no transfer hydrogenation of D-glucosone was observed.

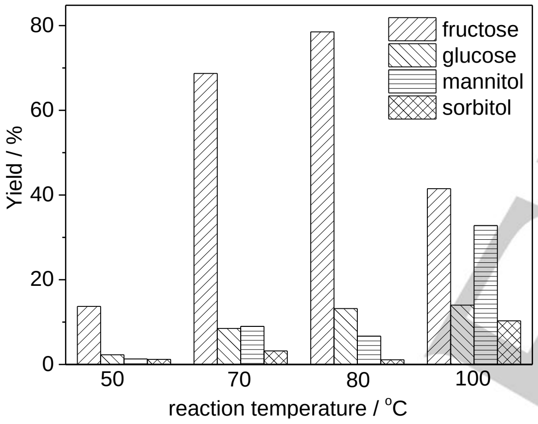


**Figure 2**. Effect of reaction temperature of Ni/C-catalyzed hydrogenation of D-glucosone.

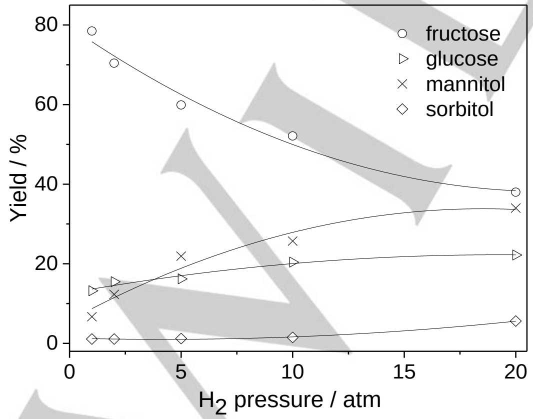


**Figure 3**. Effect of $H_2$ pressure of Ni/C-catalyzed hydrogenation of D-glucosone.

The hydrogenation of D-glucosone over Ni/C as a function of time by HPLC was monitored under the optimized conditions (80 $^oC$, 1 atm $H_2$, 7:1 EtOH/$H_2O$). Over the first 11 h of the reaction, 98.8% conversion was observed in Figure 4, where fructose, glucose, mannitol and sorbitol were generated steadily over time to reach 77.1%, 10.8%, 8.1% and 1.2% yields, respectively. The production of D-fructose was much faster than the formation of other products. The formation of fructose follows first order kinetics at 60-80 $^oC$, consistent with the hydrogenation process.[23] The rate constants were measured at 60 $^oC$ ($k$ = 0.0102 $h^{-1}$), 65 $^oC$ ($k$ = 0.0267 $h^{-1}$), 70 $^oC$ ($k$ = 0.0399 $h^{-1}$), 75 $^oC$ ($k$ = 0.0595 $h^{-1}$) and 80 $^oC$ (0.234 $h^{-1}$) (SI). Obviously, at temperature of 60-75 $^oC$, the increase in reaction rate with increase in temperature is limited, while at 80 $^oC$ a sudden increase in the reaction rate was observed, probably because of the attenuation of mass transport limitation.[23b]

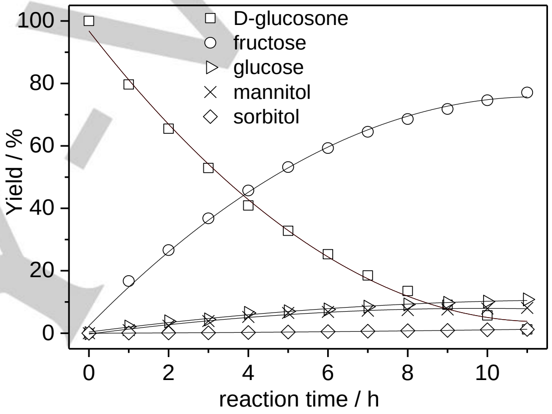
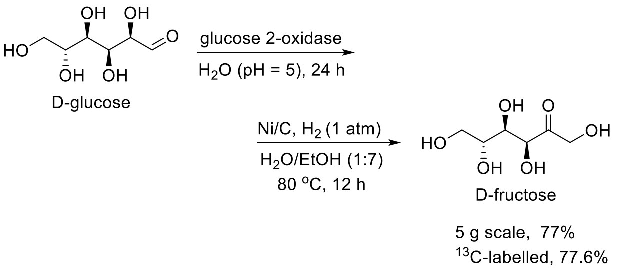


**Figure 4.** Time profile of the hydrogenation of D-glucosone under optimized conditions.

The recycling stability of the metal catalysts is important for their potential applications in industry. Initially, the spent Ni/C was subjected to simple washing and was used directly in the following cycle, which showed a decreased activity in hydrogenation of D-glucosone (85% conversion). In such a case, the selectivity towards D-fructose remained unaltered (75%). To recuperate the catalyst, a $H_2$-thermal treatment was conducted at 400 $^oC$ for 2 h. As a result, performing this $H_2$-treatment almost recovered the performance of the spent Ni/C in 10st run, which gave a complete conversion of D-glucosone with observation of 73.2% yield of D-fructose (Table S4). The Ni contents were determined as 4.8 wt % after ten cycles based on ICP analysis, close to the initial Ni content 5.0 wt %.

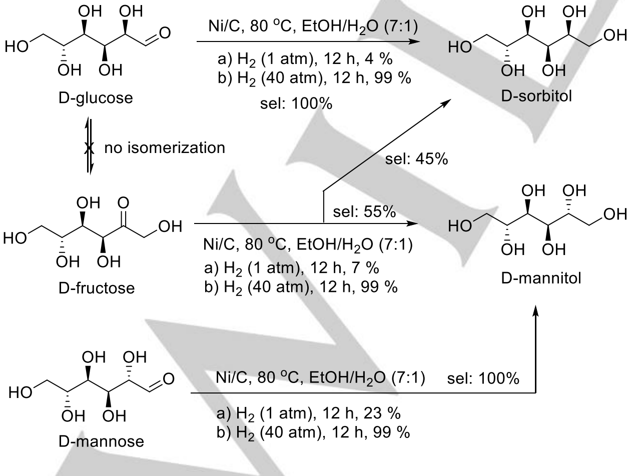
Based on above results, a one-pot procedure for preparation D-fructose was tested on a large scale (Scheme 2). Treatment of 5 g D-glucose with glucose 2-oxidase (100 mg, 2 wt%) in a citric acid butter under air for 24 h gave D-glucosone aqueous solution. After concentration and addition of EtOH and Ni/C, D-glucosone (0.28 M in 7:1 EtOH/$H_2O$), without prior isolation, was then hydrogenated into D-fructose in 77% yield under 1 atm $H_2$. Obviously, the residuary citric acid and enzyme do not affect the activity and selectivity of hydrogenation reaction. A complementary reaction by using D-glucose-$^{13}C_6$ as a substrate was conducted by this one-pot process, which gave D-fructose-$^{13}C_6$ in 77.6% yield. In the $^{13}C$ NMR spectrum ($CD_3OD/D_2O$), the C2 of $\alpha$-D-fructofuranose, $\beta$-D-fructofuranose and $\beta$-D-fructopyranose resonate characteristically at $\delta$ = 104.9 (dd, $J$ = 49.2, 49.3 Hz), 102.2 (dd, $J$ = 49.5, 46.8 Hz) and 98.5 (dd, $J$ = 48.1, 48.2 Hz) ppm, respectively, in line with typical values reported for $^{13}C$-labelled D-fructose.[24] The C1 of D-glucose resonate as doublets at 96.6 ($J$ = 46.4 Hz) and 92.7 ($J$ = 44.6 Hz) ppm, ascribed to β-D-glucopyranose and α-D-glucopyranose tautomers (SI).



5 g scale, 77%
$^{13}C$-labelled, 77.6%

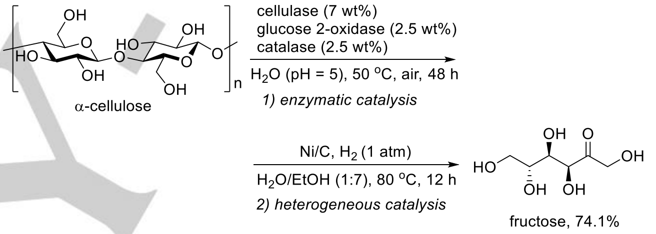
**Scheme 2**. One-pot production of fructose from glucose

To understand the products distribution in hydrogenation of D-glucosone process, we carried out a series of reactions with Ni/C in $EtOH/H_2O$ at 80 °C (Scheme 3). No isomerization reaction between D-glucose and D-fructose or D-glucose and D-mannose[20] were detected with Ni/C, differing with the acidic or basic heterogeneous catalysts. [5,7] Hydrogenation of D-glucose gave sorbitol exclusively. Obviously, the activity of this transformation was affected by $H_2$ pressure, whereas only 4% conversion was obtained under 1 atm $H_2$, versus 99% yield under 40 atm $H_2$.[23c,25] In the case of D-fructose, 45% sorbitol and 55% mannitol were generated after hydrogenation, albeit in the difference activities, consistent with previous reports.[26] Treatment of D-mannose under 1 atm and 40 atm $H_2$ with Ni/C resulted in D-mannitol in 23% and 99% yields with 100% selectivity, respectively.[16] These results may explain the reason of low yield of D-mannose and relative higher yield D-mannitol compared to D-sorbitol in Ni/C-catalyzed D-glucosone hydrogenation.



**Scheme 3**. Reactivities and selectivity of hydrogenation of sugars with Ni/C.

Since D-glucose is available from starch or cellulose *via* hydrolysis, we then explored the direct conversion of upstream substrates into D-glucose by combination of enzymatic and heterogeneous catalysis in a one-pot manner. This procedure involved treatment of $\alpha$-cellulose with cellulase (7 wt%), glucose 2-oxidase (2.5 wt%) and catalase (2.5 wt%) in citric acid butter (pH = 5) at 50 °C under air for 48 h, followed by further 12 h hydrogenation reaction with Ni/C under optimized conditions,[27] without separation of D-glucose and D-glucosone intermediates. As a consequence, fructose was obtained in 74.1% yield, together with the formation of with glucose (15.3%), mannitol (7.3%), sorbitol (2.1%) and mannose (0.6%) as byproducts (Scheme 4). Starting from starch, D-fructose was also obtained in 74.3% yield *via* hydrolysis, oxidation and hydrogenation with similar activity and selectivity (SI).



**Scheme 4**. Direct conversion of $\alpha$-cellulose into fructose by combination of enzymatic and heterogeneous catalysis.

In summary, we demonstrated a one-pot, two-step reaction procedure involving enzyme-catalyzed oxidation of D-glucose and Ni/C-catalyzed hydrogenation of D-glucosone, thus giving D-fructose in 77% yield on a large scale. Direct use of upstream substrates such as $\alpha$-cellulose and starch was also applicable in this integrated system. This constitutes an efficient protocol to produce D-fructose from biomass-derived substrates, being superior to enzyme or chemicals-catalyzed isomerization reactions in terms of efficiency and the reduction of purification. The influences on reaction temperature, time and $H_2$ pressure together with a series of catalytic hydrogenation reactions offered important information for understanding the distribution of hydrogenation products from D-glucosone.

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**Keywords:** glucose • fructose • glucose 2-oxidase • Ni/C • biomass

[1] L. M. Hanover, J. S. White, *Am. J. Clin. Nutr*. **1993**, *58*, 724S-732S.

[2] For selected reviews, see: a) R.-J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres, J. G. de Vries, *Chem. Rev.* **2013**, *113*, 1499-1597; b) M. J. Climent, A. Corma, S. Iborra, *Green Chem.* **2014**, *16*, 516-547; c) T. Wang, M. W. Nolte, B. H. Shanks, *Green Chem.* **2014**, *16*, 548-572; d) J. N. Chheda, G. W. Huber, J. A. Dumesic, *Angew. Chem*. 2007, 119, 7298-7318; *Angew. Chem. Int. Ed.* **2007**, *46*, 7164-7183.

[3] For selected examples, see: a) H. Zhao, J. E. Holladay, H. Brown, Z. C. Zhang, *Sci*e**nce** **2007**, *316*, 1597-1600; b) Y. Roman-Leshkov, C. J. Barrett, Z. Y. Liu, J. A. Dumesic, *Nature* **2007**, *447*, 982-985; c) J. B. Binder, R. T. Raines, *J. Am. Chem. Soc*. **2009**, *131*, 1979-1985; d) H. Cai, C. Li, A. Wang, T. Zhang, *Catal. Today*. **2014**, *234*, 59-65.

[4] USDA (2017) *Sugar and Sweeteners*: Market Outlook in https://www.ers.usda.gov/topics/crops/sugar-sweeteners/market-outlook/

[5] a) O. Misset, In *Handbook of Food Enzymology* (Eds.: J. R. Whitaker, A. G. J. Voragen, D. W. S. Wong), Marcel Dekker: New York, 2003, pp 1057; b) K. Buchholz, J. Seibel, *Carbohydr. Res.* **2008**, *343*, 1966-1979; c) Y. B. Tewari, *Appl. Biochem. Biotech.* **1990**, *23*, 187-203; d) H. Li, S. Yang, S. Saravanamurugan, A. Riisager, *ACS Catal.* **2017**, *7*, 3010-3029.

[6] For selected reviews, see: a) Y. Román-Leshkov, M. E. Davis, *ACS Catal*. **2011**, *1*, 1566-1580; b) S. Zhao, X. Guo, P. Bai, L. Lv, *Asian J. Chem*. **2014**, *26*, 4537; c) I. Delidovich, R. Palkovits, *ChemSusChem* **2016**, *9*, 547-561.

[7] For selected examples, see: a) M. Moliner, Y. Román-Leshkov, M. E. Davis, *Proc. Natl. Acad. Sci. U. S. A*. **2010**, *107*, 6164-6168; b) Y. Román-Leshkov, M. Moliner, J. A. Labinger, M. E. Davis, *Angew. Chem*. **2010**, *122*, 9138; *Angew. Chem. Int. Ed*. **2010**, *49*, 8954-8957; c) R. Bermejo-Deval, R. S. Assary, E. Nikolla, M. Moliner, Y. Román-Leshkov, S.-J. Hwang, A. Palsdottir, D. Silverman, R. F. Lobo, L. A. Curtiss, M. E. Davis, *Proc. Natl. Acad. Sci. U. S. A*. **2012**, *109*, 9727-9732; d) J. Dijkmans, D. Gabriels, M. Dusselier, F. de Clippel, P. Vanelderen, K. Houthoofd, A. Malfliet, Y. Pontikes, B. F. Sels, *Green Chem.* **2013**, *15*, 2777-2785; e) J. Ohyama, Y. Zhang, J. Ito, A. Satsuma, *ChemCatChem* **2017**, *9*, 2864-2868; f) C. G. Yoo, N. Li, M. Swannell, X. Pan, *Green Chem.* **2017**, *19*, 4402-4411.

[8] For selected examples, see: a) C. Liu, J. M. Carraher, J. L. Swedberg, C. R. Herndon, C. N. Fleitman, J.-P. Tessonnier, *ACS Catal*. **2014**, *4*, 4295-4298; b) J. M. Carraher, C. N. Fleitman, J.-P. Tessonnier, *ACS Catal*. **2015**, *5*, 3162-3173; c) N. Deshpande, L. Pattanaik, M. R. Whitaker, C.-T. Yang, L.-C. Lin, N. A. Brunelli, *J. Catal.* **2017**, *353*, 205-210; d) Q. Yang, W. Lan, T. Runge, *ACS Sustainable Chem. Eng.* **2016**, *4*, 4850-4858.

[9] a) I. Delidovich, R. Palkovits, *Green Chem*. **2016**, *18*, 5822-5830; b) J. F. Mendicino, *J. Am. Chem. Soc*. **1960**, *82*, 4975-4979.

[10] a) A. J. Shaw, G. T. Tsao, *Carbohydr. Res*. **1978**, *60*, 327; b) S. Despax, B. Estrine, N. Hoffmann, J. Le Bras, S. Marinkovic, J. Muzart, *Catal. Commun.* **2013**, *39*, 35-38.

[11] S. Saravanamurugan, M. Paniagua, J. A. Melero, A. Riisager, *J. Am. Chem. Soc*. **2013**, *135*, 5246-5249.

[12] For selected reviews and examples, see: a) P. N. R. Vennestrøm, C. H. Christensen, S. Pedersen, J.-D. Grunwaldt, J. M. Woodley, *ChemCatChem* **2010**, *2*, 249-258; b) I. Wheeldon, P. Christopher, H. Blanch, *Curr. Opin. Biotech*. **2017**, *45*, 127-135; c) M. Makkee, A. P. G. Kieboom, H. V. Bekkum, J. A. Roels, *J. Chem. Soc.*, *Chem. Commun.* **1980**, 930-931; d) R. Schoevaart, T. Kieboom, *Tetrahedron Lett*. **2002**, *43*, 3399-3400; e) T. J. Schwartz, S. M. Goodman, C. M. Osmundsen, E. Taarning, M. D. Mozuch, J. Gaskell, D. Cullen, P. J. Kersten, J. A. Dumesic, *ACS Catal.* **2013**, *3*, 2689-2693; f) J. M. Sperl, J. M. Carsten, J.-K. Guterl, P. Lommes, V. Sieber, *ACS Catalysis* **2016**, *6*, 6329-6334; g) A. Gimbernat, M. Guehl, M. Capron, N. L. Ferreira, R. Froidevaux, J.-S. Girardon, P. Dhulster, D. Delcroix, F. Dumeignil, *ChemCatChem* **2017**, *9*, 2080-2084.

[13] a) S. Freimund, A. Huwig, F. Giffhorn, S Köpper, *Chem. Eur. J.* **1998**, *4*, 2442-2455; b) A. Karmali, J. Coelho, *Process Biochem*. **2011**, *46*, 168-173; c) H. Seto, H. Kawakita, K. Ohto, *Biochem. Eng. J.* **2009**, 48, 36-41; d) L. W. Lai, C. L. Teo, S. Wahidin, M. S. M. Annuar, *Malays J Anal Sci* **2014**, *18*, 527-533; e) A. Karmali, J. Coelho, *Appl. Biochem. Biotechnol.* **2011**, *163,* 906-917.

[14] S. L. Neidleman, W. F. Amon, J. Geigert, *US Pat*. 4246347, **1981**.

[15] O. Ertl, M. Sut, M, Brander, *US Pat*. 2015/0353978 A1, **2015.**

[16] D. K. Mishra, J. S. Hwang, *Appl. Catal. A: Gen.* **2013**, *453*, 13-19.

[17] J. T. Liu, Y. Tang, K. G. Wu, C. F. Bi, Q. Cui, *Carbohyd. Res*. **2012**, *350*, 20-24.

[18] J. Kong, M. He, J. A. Lercher, C. Zhao, *Chem. Commun.* **2015**, *51*, 17580-17583.

[19] C. Collyer, D. Blow, *Proc. Natl. Acad. Sci. U. S. A*. **1990**, *87*, 1362-1266.

[20] The solvent polarity parameter $E_T$(30) is defined as the molar electronic transition energy (kcal $mol^{-1}$) of betaine dye 30. See: a) C. Reichardt, *Chem. Rev*. **1994**, *94*, 2319-2358; b) Y. Marcus, *Chem. Soc. Rev*. **1993**, *22*, 409-416.

[21] For a sample of epimerization of aldoses catalyzed by nickel complexes ligated with a diamine, see: S. Osanai, R. Yanagihara, K. Uematsu, A. Okumura, S. Yoshikawa, *J. Chem. Soc. Perkin Trans 2*, **1993**, 1937-1940.

[22] The reason why the highest D-fructose yield was obtained in 7:1 EtOH/$H_2O$ mixture is not yet clear. The activity and selectivity may be influenced both by solvent polarity and the solubility of $H_2$, see: M. G. Al-Shaal, W. R. Wright, R. Palkovits, *Green Chem.* **2012**, *14*, 1260-1263.

[23] a) E. Crezee, B. W. Hoffer, R. J. Berger, M. Makkee, F. Kapteijn, J. A. Moulijn, *Appl. Catal. A.* **2003**, *251*, 1-17; b) J. Wisniak, R. Simon. *Ind. Eng. Chem. Prod. Res. Dev.* **1979**, *18*, 50-57; c) X. Tan, G. Wang, Z. Zhu, C. Ren, J. Zhou, H. Lv, X. Zhang, L. W. Chung, L. Zhang, X. Zhang, *Org. Lett.* **2016**, *18*, 1518-1524.

[24] a) B. Bose, S. Zhao, R. Stenutz, F. Cloran, P. B. Bondo, G. Bondo, B. Hertz, I. Carmichael, A. S. Serianni, *J. Am. Chem. Soc*. **1998**, *120*, 11158-11173; b) T. Klepach, W. Zhang, I. Carmichael, A. S. Serianni, *J. Org. Chem*. **2008**, *73*, 4376-4387.

[25] a) P. Barbaro, F. Liguori, C. Moreno-Marrodan, *Green Chem*. **2016**, *18*, 2935-2940; b) L. Xu, W. Wei, H. Li, H. Li, *ACS Catal.* **2013**, *4*, 251-258.

[26] a) B. J. Liaw, C. H. Chen, Y. Z. Chen, *Chem. Eng. J.* **2010**, *157*, 140. b) B. Pierluigi, L. Francesca, M. M. Carmen, *Green Chem*. **2016**, *18*, 2935.

[27] In hydrogenation step, the concentration of D-glucosone is 0.07 M in 7:1 EtOH/$H_2O$.

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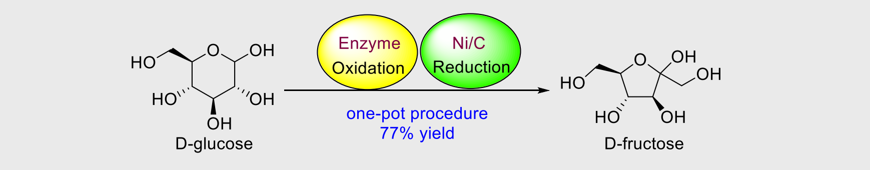
## COMMUNICATION



The combination of enzymatic and heterogeneous catalysis provides a new protocol for preparation fructose up to 77% yield from biomass-derived substrates in a one-pot manner.

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**Integration of Enzymatic and Heterogeneous Catalysis for One-pot Production of Fructose from Glucose**