Tandem catalysis for the production of alkyl lactates from ketohexoses at moderate temperatures

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Retro-aldol reactions have been implicated as the limiting steps in catalytic routes to convert biomass-derived hexoses and pentoses into valuable C2, C3, and C4 products such as glycolic acid, lactic acid, 2-hydroxy-3-butenolic acid, 2,4-dihydroxybutanoic acid, and alkyl esters thereof. Due to a lack of efficient retro-aldol catalysts, most previous investigations of catalytic pathways involving these reactions were conducted at high temperatures (≥160 °C). Here, we report moderate-temperature (around 100 °C) retro-aldol reactions of various hexoses in aqueous and alcoholic media with catalysts traditionally known for their capacity to catalyze 1,2-intramolecular carbon shift (1,2-CS) reactions of aldoses, i.e., various molybdenum oxide and molybdate species, nickel(II) diamine complexes, alkali-exchanged stannosilicate molecular sieves, and amorphous TiO2–SiO2 coprecipitates. Solid Lewis acid catalysts that are known to catalyze 1,2-intramolecular hydride shift (1,2-HS) reactions that enable the formation of α-hydroxy carboxylic acids from tetrose, triose, and glycolaldehyde, but cannot readily catalyze retro-aldol reactions of hexoses and pentoses at these moderate temperatures, are shown to be compatible with the aforementioned retro-aldol catalysts. The combination of a distinct retro-aldol catalyst with a 1,2-HS catalyst enables lactic acid and alkyl lactate formation from ketohexoses at moderate temperatures (around 100 °C), with yields comparable to best-reported chemocatalytic examples at high temperature conditions (≥160 °C). The use of moderate temperatures enables numerous desirable features such as lower pressure and significantly less catalyst deactivation.

Chemocatalytic routes for the production of α-hydroxy carboxylic acids, e.g., glycolic acid, lactic acid, 2-hydroxy-3-butenolic acid, and 2,4-dihydroxybutanoic acid, from biomass-derived sugars have been extensively investigated in the recent years, as these acids, as well as their esters and lactones, have been recognized to have a large potential to function as renewable, platform chemicals for a number of applications such as polymers, solvents, and fine chemicals (1–7). Considerable progress has been achieved with the production of lactic acid and alkyl lactates from tetrose [glyceraldehyde (GLA) and dihydroxyacetone (DHA)], with nearly quantitative yields obtained with state-of-the-art catalysis, e.g., tin-containing zeotypes Sn-Beta and Sn-MFI, which are known for their capacity to catalyze 1,2-intramolecular hydride shift (1,2-HS) reactions, at moderate temperatures (around 100 °C) (8). Similarly, the C2 and C4 products (glycolic acid, 2-hydroxy-3-butenolic acid, 2,4-dihydroxybutanoic acid, and esters thereof) can be produced in good yields when glycolaldehyde, glyoxal, or tetrose (erythrose, threose, and erythrulose) are used as substrates (4, 6). However, the substrates required for these reactions are not easily obtained or isolated from biomass, as the majority of terrestrial biomass comprises cellulose and hemicellulose (polymers of hexoses and pentoses) (5).

To enable the formation of these C2–C4 α-hydroxy carboxylic acids from cellulose and hemicellulose biomass, retro-aldol reactions are required to fragment the hexose and pentose carbon backbones (r2 and r1 in Fig. 1). For the common aldoses and ketoses, these C–C bond-splitting reactions have large activation energies and unfavorable thermodynamics at low-to-moderate temperatures. As a result, most attempts at the catalytic production of C2–C4 α-hydroxy carboxylic acids from hexoses and pentoses have involved high temperatures (≥160 °C) (3, 9). Carbon basis yields of ~64–68% of methyl lactate at full conversion were reported for reactions of sucrose catalyzed by Sn-Beta at 160 °C for 20 h (3). Lower yields of ~40–44% were reported for monosaccharide substrates in the same study (3). Recently, methyl lactate yields upwards of 75% from sucrose were achieved with Sn-Beta at 170 °C, when specific amounts of alkali carbonates were added to the reaction system (9). Furthermore, the authors suggested that, in the initial study involving Sn-Beta, materials were possibly contaminated by alkali during synthesis, and that alkali-free Sn-Beta recently led to lower yields (30%) (9).

Low thermal stability of sugars at high temperatures and lack of substrate and reaction specificity of the catalytic sites investigated in the aforementioned systems likely lead to dehydration reactions of ketohexoses to 5-hydroxymethyl furfural (5-HMF) (r5 in Fig. 1). The subsequent fragmentation and coupling reactions of 5-HMF can lead to the formation of insoluble humins that deposit on the catalyst, thereby leading to deactivation and loss of yield of useful products. Large-pore catalysts like Sn-Beta can promote aldose–ketose isomerization reactions (r1 in Fig. 1) of substrates as large as disaccharides (10) because the Lewis acid sites that are active for 1,2-HS reactions are accessible to such species. The same Lewis acid sites have been previously proposed as the active sites in retro-aldol reactions (8). This inability of Sn-Beta (and other 12-MR materials) to perform size-dependent reaction discrimination results in aldose–ketose interconversion and parallel retro-aldol reactions of aldohexoses and ketohexoses. Thus, even when ketohexose substrates are used, C3 and C4 products derived from aldoses concomitantly form with the more desired C3 products derived from ketoses (r2 and r7–r10 in Fig. 1, respectively) (3). Because of these features, catalytic strategies that allow for retro-aldol reactions of hexoses to proceed in the

Significance

Retro-aldol reactions of biomass-derived monosaccharides enable the production of a number of industrially relevant, renewable platform chemicals (e.g., C2–C4 α-hydroxy carboxylic acids, acrylic acid, and esters thereof; and ethylene and propylene glycol). Here, we show a set of retro-aldol catalysts that can perform these reactions at significantly lower temperatures (~100 °C) than previously reported, and demonstrate that these catalysts enable the key retro-aldol step when used in combination with a 1,2-hydride shift catalyst to create a reaction cascade that converts ketohexoses to lactic acid. The use of moderate temperatures enables numerous desirable features such as lower pressure and significantly less catalyst deactivation.

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absence of aldose–ketose isomerization would be highly useful, as they would have the potential to significantly affect the distribution of C₂, C₃, and C₄ products.

Here, we report moderate-temperature (around 100 °C) retro-aldol reactions of various hexoses in aqueous and alcoholic media with catalysts traditionally known for their capacity to catalyze 1,2-intramolecular carbon shift (1,2-CS) reactions of aldoses, i.e., various molybdenum oxide and molybdate species, nickel(II) diamine complexes, alkali-exchanged stannosilicate molecular sieves, and amorphous TiO₂–SiO₂ coprecipitates. Because these catalysts do not readily catalyze aldose–ketose interconversion through 1,2-HS, they are candidate cocatalysts for reaction pathways that benefit from aldose- or ketose-specific, retro-aldol fragmentation. Here, these retro-aldol catalysts are combined with solid Lewis acid catalysts to enable the moderate-temperature conversion of hexoses into α-hydroxy carboxylic acids.

**Results and Discussion**

**Retro-Aldol Reactions and 1,2-CS Catalysts.** During our recent investigation of epimerization reactions of aldohexoses on alkali-exchanged Sn-Beta materials, a change in the reaction pathway from a 1,2-HS to a 1,2-CS upon alkali exchange was observed (11). This 1,2-CS pathway in aldohexoses is analogous to those previously reported for molybdate- and nickel(II) diamine-catalyzed reactions of these aldoses (also known as Bilik reaction), where simultaneous C–C bond-breaking and -forming steps were proposed to occur (SI Appendix, Scheme S1) (12, 13). Reactions of ketoses catalyzed by molybdates and nickel(II) diamines were found to proceed through analogous pathways to form branched sugars [2-C-(hydroxymethyl)-aldoses] (r₁₁ in Fig. 1) (14–16). In addition to the branched sugars, small amounts of ketose isomers were observed, e.g., when D-fructose was reacted with molybdate, the branched sugar D-hamamelose formed, as well as small quantities of ketose isomers: sorbose, psicose, and tagatose (14, 17). The formation of ketose isomers was attributed to competing hydride shift side reactions (17).

Like with molybdates, we observed the formation of the same branched sugar (D-hamamelose) and ketose isomers when fructose was reacted with alkali-exchanged Sn-Beta at 100 °C. Interestingly, small quantities of the retro-aldol products, DHA and GLA, were also observed in the high-performance liquid chromatography (HPLC) chromatograms and nuclear magnetic resonance (NMR) spectra of unseparated reaction solutions. The presence of DHA and GLA raises questions about the mechanism of ketose isomer formation, as it is possible to form all of the ketohexoses through nonstereospecific aldol condensation of DHA and racemic GLA.

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When water-dissolved MoO₃ (H₂MoO₄) was tested as a catalyst with fructose as substrate (reacted at 100 °C), initial formation of hamamelose, DHA, and GLA was observed. Subsequently, sorbose, tagatose, and psicose appeared, without significant changes in the DHA and GLA concentration. Quantification of products was not performed due to a multitude of partially overlapping peaks in HPLC chromatograms and NMR spectra. However, fructose and sorbose were eventually observed in substantially greater quantities than tagatose, psicose, and hamamelose. Fractionation of product solutions and ¹H and ¹³C NMR were used to confirm the presence...
of DHA, GLA, fructose, sorbose, tagatose, psicose, and 2-C-(hydroxymethyl)-aldopentoses (SI Appendix, Figs. S1–S6). These results suggest that some of the ketose isomers may form as aldol condensation products of DHA and GLA, rather than directly from fructose through hydrate shift reactions, as was previously hypothesized. The unfavorable equilibria of retro-aldol reactions at these moderate temperatures may be responsible for the low concentrations of DHA and GLA. The reverse reaction, aldol coupling, is a logical secondary reaction that can form the more stable ketohexose side products. The possibility of aldol coupling was confirmed by reacting a mixture of DHA and GLA under the same conditions, resulting in complex mixture of products containing ketohexoses and 2-C-(hydroxymethyl)-aldopentoses.

Although the low production of 2-C-(hydroxymethyl)-aldopentoses may be due to thermodynamic limitations, e.g., hamamelose-fructose equilibrium \( K_{eq} \sim 14 \) (14), tagatose and psicose may form in small quantities due to kinetic reasons. The tetradentate open-chain ketohydrol fructose–molybdate complex that was previously hypothesized to be the key species in the fructose–hamamelose rearrangement catalyzed by water-dissolved molybdates is shown in SI Appendix, Scheme S2 (along with analogs for other ketohexoses) (14). \(^1\)H and \(^13\)C NMR studies of the molybdate complexes of ketohexoses suggest that only fructose and sorbose form detectable amounts of tetradentate molybdate complexes, whereas psicose and tagatose tend to form tridentate complexes (18). These results suggest that aldol coupling reactions that would lead to the formation of tagatose and psicose would proceed through more energetic transition states, with slow kinetics. Furthermore, psicose and tagatose complexes appear more stable, with 80–95% of the sugars bound to Mo (at stoichiometric Mo/monosaccharide amounts), whereas these values for sorbose and fructose are only 15–20% (18). If the retro-aldol reactions of ketohexoses proceed through tetradentate molybdate complexes, these results suggest that the formation of tagatose and psicose may reduce the formation of catalytically active molybdate species through competitive binding and formation of tridentate complexes.

Although binuclear molybdate species were implicated in epitmerization reactions catalyzed by water-dissolved MoO\(_3\), higher structures containing molybdate ions were later shown to also catalyze epitmerization reactions, e.g., Keggin structure molybdenum-based polyoxometalates (19), and heptamolybdate species were previously shown to catalyze the 1,2-CS in aldoses (13) and 2-C-(hydroxymethyl)-aldopentose formation from ketohexoses (16) at temperatures around 100 °C. We observed that \([\text{Ni(N,N,N',N'-Me$_2$en)$_3$}]\text{Cl}_2\) in methanol also accelerated the retro-aldol part of the methyl lactate-producing reaction cascade at temperatures around 100 °C.

**Coupling Retro-Aldol Reactions with 1,2-HS for Lactate Production.** Materials that can catalyze the 1,2-CS in aldoses were reported to be poor 1,2-HS catalysts for the same substrates, as the production of ketoses was not detected (17). Because the formation of lactate from trioses by Lewis acid catalysts has been shown to involve a 1,2-HS (\(r_\text{3}\) in Fig. 1) (24), an efficient route to the more thermodynamically stable lactate products is not enabled by the retro-aldol catalysts described above (resulting in triose accumulation and recombination through aldol reactions). Addition of a 1,2-HS cocatalyst [Sn-MFI with Si/Sn = 70 ± 6, fluoride-free synthesis (25)] to a 1 wt% fructose, 0.2 wt% MoO\(_3\) aqueous solution enabled formation of lactic acid at 100 °C. However, \(^1\)H NMR data suggest that the lactate formed complex with molybdate species (SI Appendix, Fig. S7), and that lactate production stopped once the stoichiometric amount of 2 mol of lactate per mole of molybdate was produced. This inhibition of catalysis by product coordination is consistent with the previously reported pH-dependent molybdate–lactate complex formation, with an estimated pK of formation of ~49 at pH = 4.5 (26).

When the reactions of fructose with MoO\(_3\) and Sn-MFI were performed in alcoholic media, corresponding alkyl lactates were produced in good yields (see Fig. 2 for a representative graph of ethyl lactate production from fructose as a function of time at different temperatures, SI Appendix, Fig. S8, for \(^1\)H NMR of methyl lactate product, and Table 1 for the maximum observed yields of lactate products under various reaction conditions). Turnover numbers (TONs) in excess of unity indicate that alkyl lactate is produced in excess of the stoichiometry of the reaction.

![Fig. 2. Ethyl lactate yield as a function of time at different temperatures (indicated in legend). Reaction conditions were as follows: 80 mg of MoO\(_3\), 100 mg of Sn-MFI, 50 mg of o-fructose, 4.9 g of EtOH, and 50 mg of naphthalene as internal standard.](image-url)
lactate production is truly catalytic in such reactions, e.g., for reaction 6 in Table 1, the TON ≥ 5.5 based on Mo atoms for the retro-aldol reaction of fructose, and TON ≥ 16.1 based on Sn atoms for lactate formation from the resulting trioses. For reactions performed in alcoholic media, MoO3 particles remained undissolved and progressively turned a dark-blue color, suggesting an increasing rate of ethyl lactate formation. Ultimately, ethyl lactate yield was not significantly impacted, suggesting that side reactions of this reaction network. Time-dependent reaction profiles of alkyl lactate products and gain further insight into the limiting factors of this reaction network.

We investigated a number of parameters to maximize the yield of alkyl lactate products and gain further insight into the limiting factors of this reaction network. Time-dependent reaction profiles like those shown in Fig. 2 for the reactions accomplished and described in the following discussion are in SI Appendix, Figs. S9–S18. Data in Fig. 2 (reactions 1–4 in Table 1) show that, at otherwise-fixed conditions, increase in temperature resulted in an increased rate of ethyl lactate formation. Ultimately, ethyl lactate yield was not significantly impacted, suggesting that side reactions may have comparable activation energies to the limiting steps in lactate production. At 100 °C, with constant Sn-MFI amount, increasing the amount of MoO3 catalyst led to a faster approach to the maximum lactate yield, but the increase in rate was not proportional to the change in MoO3 amount (reactions 2, 5, and 6 in Table 1, and SI Appendix, Fig. S9). Additionally, a potential induction time is observed for the reaction with the lowest MoO3 content. Conversely, fixing the amount of MoO3, and varying the amount of Sn-MFI suggested that two regimes are possible: one where the ethyl lactate production is limited by retro-aldol reactions, i.e., excess Sn-MFI catalyst can deplete trioses faster than they are generated, and the other where the ethyl lactate production from trioses is kinetically relevant, i.e., insufficient Sn-MFI leads to accumulation of trioses (reactions 2, 7, and 8 in Table 1, and SI Appendix, Fig. S10). In the former scenario, the ultimate yield of ethyl lactate is higher than in the latter. Similarly, at fixed amounts of both catalysts, lower initial substrate concentrations result in higher ethyl lactate yields (reactions 2, 9, and 10 in Table 1, and SI Appendix, Fig. S11). These data suggest that high concentrations of substrate and intermediates are conducive to side-product formation and that rapid conversion to stable alkyl lactate products can reduce the extent of irreversible side reactions.

A set of control experiments that illustrate the importance of the combination of the two catalysts were performed (reactions 2 and 11–14 in Table 1, and SI Appendix, Fig. S12). In the absence of MoO3 cocatalyst, Sn-MFI is unable to convert fructose to

### Table 1. Maximum observed yields of lactic acid or alkyl lactates obtained under various reaction conditions

<table>
<thead>
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<th>Reaction</th>
<th>1,2-CS catalyst, mass/mg</th>
<th>1,2-HS catalyst, mass/mg</th>
<th>Substrate, wt%</th>
<th>Solvent</th>
<th>Temperature, °C</th>
<th>Maximum yield, carbon basis, %</th>
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Reactions were performed in 10-mL thick-walled crimp-sealed glass reactors that were heated in a temperature-controlled oil bath. Aliquots (~100 µL) were extracted and filtered with a 0.2-µm polytetrafluoroethylene syringe filter before analysis. Reaction conditions: for each reaction, the catalyst amounts, substrate concentrations, solvents, and temperature used are indicated in the table. Each reaction involving alcoholic solvents was performed with 4.9 g of solvent and 50 mg of naphthalene as internal standard for GC-FID quantification.

*For reactions with [Ni(NW,NW,N′-Me4en)]Cl2, aliquots were agitated with 20 mg of Dowex 50WX2 (hydrogen form) resin to remove nickel(II) species before filtration.

†For the reaction performed in water, no naphthalene was added, and 4,4-dimethyl-4-silapentane-1-sulfonic acid, sodium salt (DSS) was used as an external standard for quantitative 1H-NMR.
ethyl lactate in significant yields, even though high yields of ethyl lactate are rapidly achieved by Sn-MFI alone when an equimolar mixture of DHA and GLA are used as substrates. Conversely, without Sn-MFI, MoO₃ slowly catalyzes the formation of ethyl lactate from fructose, with an ultimate ethyl lactate yield being considerably lower than in the mixed-catalyst system. Additionally, the use of equimolar DHA and GLA mixture as starting substrate does not result in significantly higher yields of ethyl lactate when MoO₃ is used by itself, further illustrating the rapidity of side reactions of trioses when a catalytic path to the thermodynamically stable lactate products is not present.

As discussed above, other Mo-containing 1,2-CS catalysts, e.g., MoO₂, MoS₂, H₂PMo₁₀O₄₀, Na₂MoO₄, (NH₄)₆Mo₇O₂₄·4H₂O, ZnMoO₄, and CaMoO₄, were also able to accelerate alkyl lactate production from fructose when paired with Sn-MFI (reactions 15–17 in Table 1, and SI Appendix, Fig. S13, for the first three). Although the conditions for these catalysts have not been optimized, all alternative Mo-containing catalysts resulted in lower ethyl lactate yields than those achieved with MoO₃. Similarly, [Ni(N₂N₂N₂N₂-\text{Me}₄\text{en})₂⁺Cl₂ in methanol also accelerated the retro-aldol part of the reaction cascade at 100 °C (reactions 18 and 19 in Table 1, and SI Appendix, Fig. S14), but deactivated after a few turnovers, in agreement with deactivation observed for aldose epimerization for similar complexes (13). This deactivation is potentially related to the formation of a white precipitate that was observed when [Ni(N₂N₂N₂N₂-\text{Me}₄\text{en})₂⁺Cl₂ dissolved in MeOH was allowed to stand at ambient temperatures for extended times. Although nickel(II) diamines do not appear to be stable catalysts at reaction conditions, they are exceptionally active 1,2-CS catalysts (with 1,2-CS reactions of aldoses observed as low as 25 °C), and may be good model systems for retro-aldol reactions catalyzed by 1,2-CS catalysts, as their sugar complexes are isolable and amenable to characterization through extended X-ray absorption fine structure (EXAFS) analysis and X-ray crystallography (13). Amorphous TiO₂–SiO₂ coprecipitates were reported to slowly catalyze the 1,2-CS of glucose in methanol (10). Here, we observed only a minor increase in lactate production upon addition of TiO₂–SiO₂ coprecipitate to Sn-MFI (reaction 20 in Table 1, and SI Appendix, Fig. S14), and its use was not further investigated.

Sn-Beta [Si/Al = 95 ± 14, Fluoride synthesis (27)] can be used in place of Sn-MFI for the second part of the reaction cascade (reactions 21–22 in Table 1, and SI Appendix, Fig. S15). Furthermore, when coupled with MoO₃ under conditions where lactate formation from trioses was kinetically relevant, Sn-Beta performed better than Sn-MFI. This result is consistent with the reported faster kinetics of alkyl lactate synthesis from trioses by Sn-Beta than Sn-MFI (8). Because Sn-Beta can also catalyze glucose–fructose–mannose isomerization reactions through the 1,2-HS and, to some degree, retro-aldol reactions of hexoses, Sn-Beta was not used as the catalyst of choice in the current study, to avoid additional complicating factors in the reaction network. To illustrate this point, data in SI Appendix, Fig. S15, corresponding to reaction 22 in Table 1, show ethyl lactate formation from glucose when Sn-Beta is used in combination with MoO₃, thus indicating that aldose–ketose isomerization reactions occur on kinetically relevant timescales. Another noted benefit of using Sn-MFI as the 1,2-HS catalyst is that it can be easily synthesized in the absence of fluoride (25) (a frequently raised concern for large-scale syntheses of catalysts to be used for biomass processing, e.g., Sn-Beta). In principle, even more economically accessible materials that can catalyze lactate formation from trioses, e.g., postsynthetically treated Ti zeolites (28) or homogeneous Lewis acids (29), may be paired with the retro-aldol catalysts reported in this study to produce alkyl lactates from hexoses at mild conditions.

Sn-Beta (and other Lewis acid-containing zeotypes, e.g., Ti-Beta) has also been shown to catalyze the 1,2-CS reactions of aldoses in aqueous solutions when either borate (30) or alkali salts (11) are present. The recently reported increase in methyl lactate production by Sn-Beta from fructose in methanol at 170 °C (from 16% to 57%) upon alkali carbonate addition (9) is consistent with formation of 1,2-CS sites upon alkali exchange of open sites in Sn-Beta. Sn-Beta systems with added borate and alkali salts were reported to be pH sensitive and are not efficient 1,2-CS catalysts in acidic conditions (11, 30). Furthermore, if Sn-MFI is used as a size-dependent 1,2-HS catalyst in conjunction with borate- or alkali-modified Sn-Beta, borate or alkali ions have the capacity to enter the Sn-MFI pores and influence the efficiency of lactate production from trioses. Thus, coupling of lactic acid or alkyl lactate production with retro-aldol reactions in mixed Sn-based zeotype systems was not studied here, but may warrant further investigation for the potential to affect the distribution of C₂, C₃, and C₄ products by limitation of aldose–ketose interconversion.

Formation of other 2-ketohexoses and 2-C-(hydroxymethyl)-aldopentoses in MoO₃-catalyzed reactions of fructose is discussed above. The differences in interactions between the various molybdate and hexose species may impact the rate of retro-aldol reactions. To test for this possibility, psicose, sorbose, tagatose, and hamamamlose were reacted under the same conditions as fructose (reactions 24–27 in Table 1, and SI Appendix, Fig. S16). The rate of ethyl lactate formation from hamamamlose is closely identical to that from fructose. The initial rates of ethyl lactate formation from sorbose and psicose are lower than from fructose, but comparable ultimate yields of ethyl lactate are observed. Tagatose appears to be the slowest to react. Although it is clear that formation of ketohexose side products can impact the ultimate kinetics of ethyl lactate production, it is not certain whether the difference in the rates of retro-aldol reactions among these substrates is due to differences in energy barriers or due to reduction of available catalytic sites through competitive coordination in binding configurations that are not activated for retro-aldol reactions.

At 160 °C, Sn-Beta was reported to perform much better for lactate production from sucrose in methanol than in ethanol, isopropanol, or water (3). Here, for the case of MoO₃/Sn-MFI, no significant differences in kinetics or ultimate yields of alkyl lactates are observed between methanol and ethanol solvents, at 100 °C (reactions 2 and 28 in Table 1, and SI Appendix, Fig. S17). However, between 10 wt% and 90 wt% ethanol is used, the ultimate yield of ethyl lactate is significantly lower than for neat ethanol solvent (reactions 2 and 29 in Table 1, and SI Appendix, Fig. S17). This difference may be attributed to increased solubility of molybdate species in the mixed-solvent system. Because lactic acid forms strong complexes with molybdate ions, this fraction of lactate species is missing from the reported yield. In addition to the main alkyl lactate products quantified in this study, species consistent with retro-aldol reactions on aldohexoses and partially oxidized products were identified in the gas chromatography (GC)–mass spectrometry (MS) chromatograms of reaction solutions, e.g., ethyl acetal and ethyl esters of glycolaldehyde, glycolic acid, pyruvic acid, 2-hydroxy-3-butenoic acid, and 2,4-dihydroxybutanoic acid were observed for reactions in ethanol. Catalyst combinations that did not rapidly convert ketoses into alkyl lactates and generated Brønsted acidity also resulted in minor formation of 5-HMF and its partially oxidized variants, e.g., aqueous reactions of H₂PMo₁₀O₄₀ and Sn-MFI or H₂MoO₄ and Sn-MFI, after complete reduction of Mo(VI) to Mo(V) and/or Mo(IV) is reported to affect the dissection of C₂ vs. C₃ and C₄ products. The partially oxidized products may be formed by the reduction of Mo(VI) to Mo(V) and/or Mo(IV)
because particles of MoO₃ appear to progressively turn dark blue over the course of the reaction. In this regard, 1,2-CS catalysts that do not readily reduce in the presence of carbohydrates have the potential to result in higher ultimate lactate yields. Quantification of reaction intermediates and by-products under these relatively mild retro-aldol conditions and their dependence on 1,2-CS and 1,2-HS site distribution are some of our current focus. The use of moderate temperatures (~100 °C) enables numerous desirable features for the production of lactic acid and alkyl lactate from hexoses such as lower process pressure and reduced catalyst deactivation due to product deposition on the catalysts. The minimal operating pressure for such reactions is autogenous, and is largely determined by the vapor pressure (P^sat) of the solvent. For instance, for methanol, P^sat = 3.5 bar at 100 °C and P^sat = 21.9 bar at 170 °C (31). We note that, in the case of reactions in ethanol at 100 °C, after ethyl lactate production from the initially added fructose stops, e.g., see data in SI Appendix, Fig. S18, ~20 h, the MoO₃/Sn-MFI catalyst combination is still active without regeneration by calcination or washing, as indicated by further production of ethyl lactate upon introduction of additional fructose to the reaction solution. In our hands, this is contrary to the coked state of Sn-Beta catalysts that requires catalyst calcination after high-temperature reactions (3).

Materials and Methods

Reagents and Catalysts. A full list of chemicals used in this study and their sources can be found in SI Appendix. The hydrothermal syntheses of Sn-MFI and Sn-Beta molecular sieves were performed according to previously published procedures that are described in detail in SI Appendix.

Reaction Analysis. Carbohydrate analysis and fractionation were performed via HPLC on an Agilent Hi-Plex Ca column with refractive index and evaporative light scattering detectors. Alkyl lactates were quantified by GC with a flame ionization detector (FID), and naphthalene as an internal standard. Additional side products were identified by GC coupled with MS. ¹H and ¹³C liquid NMR spectrometry was used for product identification. Reactions were performed in thick-walled crimp-sealed glass reactors (VWR) that were heated in a temperature-controlled oil bath. Aliquots were extracted at desired times and analyzed by HPLC, GC, and/or NMR. Reported yields are on a carbon basis. Detailed descriptions of procedures followed during reaction testing and product identification can be found in SI Appendix.

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Supplementary Information Appendix

Experimental Methods

1. Sources of chemicals
MoO₃ (Alfa Aesar, 99.95%), MoO₂ (Sigma-Aldrich, 99%), H₃PMO₁₁O₄₀·xH₂O (Alfa Aesar), MoS₂ (Alfa Aesar, 99%), Na₂MoO₄ (Sigma-Aldrich, 98%), (NH₄)₂MoO₄·2H₂O (Alfa Aesar, 99%), NiCl₂·6H₂O (Sigma-Aldrich, ≥98%), N,N,N',N'-tetramethylethylenediamine, (Alfa Aesar, 99%), D-fructose (Sigma-Aldrich, ≥99%), L-sorbos (Sigma-Aldrich, ≥98%), D-tagatose (Sigma-Aldrich, ≥98.5%), D-psicose (Sigma-Aldrich, ≥95%), D-hamamelo (Sigma-Aldrich, ≥99.5%), D-Glucose (Sigma-Aldrich, ≥98%), D/L-glyceraldehyde (Sigma-Aldrich, ≥90%), dihydroxyacetone dimer (Alfa Aesar, ≥70%), lactic acid (Sigma-Aldrich, ≥98%), methyl lactate (Sigma-Aldrich, ≥98%), ethyl lactate (Sigma-Aldrich, ≥99%), ethanol (Koptec, anhydrous 200-proof), methanol (Sigma-Aldrich, 99.8%), naphthalene (Sigma-Aldrich, 99%), tetraethylammonium hydroxide solution (Sigma-Aldrich, 35% in water), tetraethylorthosilicate (Sigma-Aldrich, 98% (w/w)), tin (IV) chloride pentahydrate (Sigma-Aldrich, 98%), hydrofluoric acid (Sigma Aldrich, 54% (w/w) in water), tetraethylammonium fluoride dihydrate (Sigma-Aldrich, 97%), NaNO₃ (Sigma Aldrich, ≥99.0%), NaOH (Alfa Aesar 97%) were purchased and used as received. Chloride form of Amberlite IRA-400 (Sigma-Aldrich) resin was used for immobilization of molybdate salts. TiO₂–SiO₂ co-precipitate (type III, No. 2) was obtained from W. R. Grace (Si/Ti = 56) and was calcined in flowing air (100 mL min⁻¹, Air Liquide, breathing grade) at 580 °C (ramped up at 1 °C min⁻¹) for 6 h prior to use.

2. Synthesis of materials

Synthesis of Sn-Beta
Sn-Beta was synthesized according to previously reported procedures (1), as follows: 15.25 g of tetraethylammonium hydroxide solution (35% (w/w) in water) were added to 14.02 g of tetraethylorthosilicate, followed by the addition of 0.172 g of tin (IV) chloride pentahydrate. The mixture was stirred until tetraethylorthosilicate was completely hydrolyzed and then allowed to reach the targeted H₂O:SiO₂ ratio by complete evaporation of ethanol and partial evaporation of water. Next, 1.53 g of hydrofluoric acid (54% (w/w) in water) were added, resulting in the formation of a thick gel. The final molar composition of the gel was 1 SiO₂ / 0.0077 SnCl₄ / 0.55 TEAOH / 0.54 HF / 7.52 H₂O. As-synthesized Si-Beta (vide infra) was added as seed material (5 wt% of SiO₂ in gel) to this gel and mixed. The final gel was transferred to a Teflon-lined stainless steel autoclave and heated at 140 °C in a static oven for 25 days. The recovered solids were centrifuged, washed extensively with water, and dried at 100 °C overnight. The dried solids were calcined in flowing air (100 mL min⁻¹, Air Liquide, breathing grade) at 580 °C (ramped up at 1 °C min⁻¹) for 6 h.

Synthesis of Si-MFI
Si-MFI was synthesized with slight modifications to method A reported by Mal et al. (2), as follows: 0.92 g of tin (IV) chloride pentahydrate in 6.08 g of water added to 28.00 g of tetraethylorthosilicate and stirred (uncovered) for 30 min. Next, 48.21 g of tetrapropylammonium hydroxide solution (25% (w/w) in water) was added to the mixture under stirring. After 1 h of additional stirring (uncovered), the remaining water was added, to achieve the final molar composition of the gel of 1 SiO₂ / 0.02 SnCl₄ / 0.45 TPAOH / 35 H₂O. The gel was stirred for an additional 30 min (covered), evenly split among three Teflon-lined stainless steel autoclaves, and heated at 160 °C in a static oven for 48 h. The solids were recovered by filtration, washed extensively with water, and dried at 100 °C overnight. The dried solids were calcined in flowing air (100 mL min⁻¹, Air Liquide, breathing grade) at 580 °C (ramped up at 1 °C min⁻¹) for 6 h.

Na-Exchange of Sn-Beta
Three successive sodium ion exchanges were performed according to previously described procedure (3) as follows: calcined Sn-Beta was stirred in a solution of 1 M NaNO₃ and 10⁻⁴ M NaOH in distilled water. Each ion exchange step was carried out for 24 hours at ambient temperature, using 45 mL of exchange or wash solution per 300 mg of starting solids. The material was recovered by centrifugation, and washed three times with 1 M NaNO₃ in distilled water. The final material was dried at ambient temperature overnight by an impinging flow of air.

H₃PW₁₂O₄₀ and (NH₄)₂MoO₄ exchanged resins
H₃PW₁₂O₄₀ and (NH₄)₂MoO₄ were immobilized by ion exchanging the chloride form of Amberlite IRA-400. In each procedure, n meq of ion capacity worth of resin was used per 1 meq of anion to be immobilized, where n is the charge of the anion. The resin was suspended in an aqueous solution of anion for 24 h, filtered, washed extensively with water, and dried at ambient temperature overnight by an impinging flow of air.
3. Reaction analysis

Carbohydrate analysis and fractionation were performed via high performance liquid chromatography on an Agilent 1200 system equipped with refractive index and evaporative light scattering detectors. An Agilent Hi-Plex Ca column held at 80 °C was used with ultrapure water as the mobile phase (flow rate of 0.6 mL min⁻¹). Quantitative GC/FID analysis of alkyl lactates was performed on an Agilent 7890B GC system equipped with a flame ionization detector and an Agilent HP-5 column. Qualitative GC/MS analysis of side-products was performed on an Agilent 5890 GC system with an Agilent 5970 mass spectrometer and an Agilent DB-5 column. Liquid ¹H and ¹³C NMR spectra were recorded with a Varian INOVA 500 MHz spectrometer equipped with an auto-x pfg broad band probe. All liquid NMR analysis was performed in D₂O solvent, with 4,4-dimethyl-4-silapentane-1-sulfonic acid (DSS) as an internal standard.

Reactions were performed in 10 mL thick-walled crimp-sealed glass reactors (VWR) that were heated in a temperature-controlled oil bath. A typical reaction procedure involved: addition of desired amount of catalysts (i.e. MoO₃, Sn-MFI, etc.), carbohydrate substrate (i.e. D-fructose, DHA, etc.), and solvent (i.e. EtOH, MeOH, etc. with pre-dissolved naphthalene as internal standard) to reactor, sealing of reactor with crimp-top, agitation of reactor at ambient temperature until dissolution of substrate, and placement of reactor in the oil bath at desired temperature. Aliquots (~100 μL) were extracted at indicated times, filtered with a 0.2 μm PTFE syringe filter, and analyzed by GC/FID. For reactions with [Ni(N,N',N',N'-Me₄en)₂]Cl₂, aliquots were agitated with 20 mg of Dowex 50WX2 (hydrogen form) resin to remove nickel (II) species prior to filtration. For product identification by HPLC, liquid NMR, or GC/MS, internal standard was excluded and the entire reactor content was used. Rotary evaporation was used to remove solvent when needed.

4. 1,2-intramolecular carbon shift in aldoses and ketoses

Scheme S1. Schematic representation of a 1,2-CS (R₂=H for aldoses or R₂=CH₂OH for ketoses, and R₁ represents the remainder of the saccharide) that involves simultaneous breaking and forming of C-C bonds.

5. Product identification by fractionation and NMR

Fructose
Reaction
Fraction

Fructose
Standard

Fig. S1. ¹H NMR spectra of D-fructose standard solution (bottom) and of the fructose-containing fraction (top) isolated after reaction of D-fructose with MoO₃ in water at 100 °C for 4 h. Sorbose is present in the collected fraction.
Fig. S2. $^1$H NMR spectra of L-sorbose standard solution (bottom) and of the sorbose-containing fraction (top) isolated after reaction of D-fructose with MoO$_3$ in water at 100$^\circ$C for 4 h.

Fig. S3. $^{13}$C NMR spectra of L-sorbose standard solution (bottom) and of the sorbose-containing fraction (top) isolated after reaction of D-fructose with MoO$_3$ in water at 100$^\circ$C for 4 h.
Fig. S4. $^1$H NMR spectra of D-psicose standard solution (bottom) and of the psicose-containing fraction (top) isolated after reaction of D-fructose with MoO$_3$ in water at 100 °C for 4 h. DHA and a 2-C-(hydroxymethyl)-aldopentose are present in the collected fraction. HDO peak ca. 4.8 ppm is digitally suppressed for clarity.

Fig. S5. $^1$H NMR spectra of D-tagatose and GLA standard solutions (bottom and middle, respectively) and of the tagatose-containing fraction (top) isolated after reaction of D-fructose with MoO$_3$ in water at 100 °C for 4 h. Glyceraldehyde is present in the collected fraction.
Fig. S6. $^1$H NMR spectra of D-Hamamelose standard solution (bottom) and of the hamamelose-containing fraction (top) isolated after reaction of D-fructose with MoO$_3$ in water at 100 °C for 4 h. DHA and an unknown are present in the collected fraction.

6. Molybdate complexes with sugars

Scheme S1. Fructose, sorbose, tagatose, and psicose tetradentate molybdate complex of fructose hypothesized to be involved in rearrangement to corresponding 2-C-(hydroxymethyl)-aldopentoses
7. $^1$H NMR evidence of lactate production by combination of MoO$_3$ and Sn-MFI

pH = 2.5

Fig. S7. $^1$H NMR spectra of methyl group in molybdate-lactate complex formed in the reaction of D-fructose with MoO$_3$ and Sn-MFI in water at 100 °C for 16 h (ca. 25% yield). Top spectrum (pH = 2.5) is of a reaction aliquot prior to pH adjustment to 7.5 (bottom spectrum) by addition of sodium bicarbonate.

pH = 7.5

Fig. S8. $^1$H NMR spectra of reaction solution of D-fructose with MoO$_3$ and Sn-MFI in MeOH at 100 °C for 30 h (ca. 68% methyl lactate yield) showing the three intense resonances of methyl lactate (ca. 1.25, 3.60, and 4.25 ppm) and small peaks associated with by-products. MeOH peak ca. 3.19 ppm is digitally suppressed for clarity.
8. Reaction profiles

**Fig. S9.** Ethyl lactate yield as a function of time for varying MoO$_3$ catalyst amounts (indicated in legend). Reaction conditions: 100 °C; 100 mg Sn-MFI; 50 mg D-fructose; 4.9 g EtOH; 50 mg naphthalene as internal standard.

**Fig. S10.** Ethyl lactate yield as a function of time for varying Sn-MFI catalyst amounts (indicated in legend). Reaction conditions: 100 °C; 80 mg MoO$_3$; 50 mg D-fructose; 4.9 g EtOH; 50 mg naphthalene as internal standard.
Fig. S11. Ethyl lactate yield as a function of time for varying concentrations of fructose (indicated in legend). Reaction conditions: 100 °C; 80 mg MoO₃; 100 mg Sn-MFI; 4.9 g EtOH; 50 mg naphthalene as internal standard.

Fig. S12. Ethyl lactate yield as a function of time for control runs illustrating the necessity of catalyst. Reaction conditions: 100 °C; catalyst amounts specified in legend; 50 mg of D-fructose (F) or mixture of 25 mg of GLA and 25 mg DHA (GLA/DHA) 4.9 g EtOH; 50 mg naphthalene as internal standard.
Fig. S13. Ethyl lactate yield as a function of time for varying Mo-containing retro-aldol catalysts (indicated in legend). Reaction conditions: 100 °C; 100 mg Sn-MFI; 50 mg D-fructose; 4.9 g EtOH; 50 mg naphthalene as internal standard.

Fig. S14. Methyl lactate yield as a function of time for MoO₃ and [Ni(N,N,N',N'-Me₄en)₂]Cl₂ catalysts (amounts indicated in legend). Reaction conditions: 100 °C; 100 mg Sn-MFI; 50 mg D-fructose; 4.9 g MeOH; 50 mg naphthalene as internal standard.
**Fig. S15.** Ethyl lactate yield as a function of time for Sn-Beta/Sn-MFI comparison. Reaction conditions: 100 °C; 80 mg MoO$_3$; Sn-Beta or Sn-MFI amount specified in legend; 50 mg of D-fructose (F), D-Glucose (G), or DHA; 4.9 g EtOH; 50 mg naphthalene as internal standard.

**Fig. S16.** Ethyl lactate yield as a function of time for different ketohexoses and a 2-C-(hydroxymethyl)-aldopentoses (hamamelose) as substrates. Reaction conditions: 100 °C; 80 mg MoO$_3$; 100 mg Sn-MFI; 50 mg of D-fructose, D-psicose, D-hamamelose, L-sorbose, or D-tagatose; 4.9 g EtOH; 50 mg naphthalene as internal standard.
Fig. S17. Lactate yield as a function of time for different solvents (specified in legend). Reaction conditions: 100 °C; 80 mg MoO₃; 100 mg Sn-MFI, 50 mg of D-fructose; 4.9 g solvent; 50 mg naphthalene as internal standard. In case of water, external standard (DSS) was used for ¹H NMR quantification instead of naphthalene.

Fig. S18. Ethyl lactate weight fraction as a function of time for batch and semibatch reactions. Reaction conditions: 100 °C; 80 mg MoO₃; 100 mg Sn-MFI; 4.9 g EtOH; 50 mg naphthalene as internal standard. For batch operation, 50 mg of D-fructose was added at t = 0 h. For semibatch operation, 50 mg of D-fructose was added at t = 0 h. After 20 h of reaction, the reactor was rapidly quenched with ice and opened. At this point, the first aliquot was taken and another 50 mg of D-fructose was added to the reactor. After re-sealing the reactor, regular operation and sampling procedure was resumed.
References

