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# Separation, Recovery and Upgrading of 2,3-Butanediol from Fermentation Broth

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## ABSTRACT

2,3-Butanediol (BDO) is a bio-derived building block available from biomass through biochemical methods in high titers (>120 g/L) making it an attractive target for production and further upgrading to chemical products and fuels such as Sustainable Aviation Fuel (SAF). A key

challenge to enable the adoption of BDO as a precursor is the effective separation and isolation of this molecule from the fermentation broth. BDO has a boiling point higher than water (177 °C), and as a consequence, separation via distillation methods is an energy intensive and therefore costly approach. We have improved the BDO separation through conversion to a 1,3-dioxolane directly in fermentation broth via reaction with bio-derived aldehydes catalyzed by a solid acid catalyst. The resulting dioxolane phase separates from the fermentation broth allowing for easy decantation and isolation in > 90 % isolated yield. Isolated dioxolane can either be used directly as a compression ignition fuel, trans-acetalized to recover high purity BDO or used directly in a catalytic process as a BDO synthon to produce methyl ethyl ketone (MEK) with aldehyde recovery in near quantitative yield.

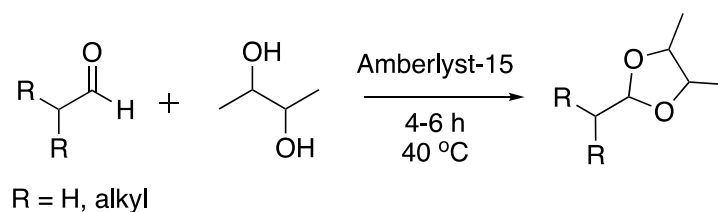
## **Introduction**

2,3-Butanediol (BDO) is a highly attractive building block<sup>1-4</sup> that can be produced in high titers of up to 120 g/L<sup>5</sup> via fermentation of biomass-derived sugars using engineered *Zymomonas mobilis* due to low toxicity to the producing microorganisms.<sup>6-12</sup> As BDO is a 4-carbon molecule, fewer energy intensive C-C bond forming reactions are needed relative to C1 and C2 building blocks (e.g. methanol and ethanol) when constructing more complex carbon scaffolds for fuel applications. The molecular structure affords the opportunity to further derivatize the molecule to produce chemical intermediates and products such as methyl ethyl ketone (MEK),<sup>13-19</sup> butadiene<sup>20</sup>,<sup>21</sup> and epoxides.<sup>22</sup> These co-products have currently available markets and could potentially enable the production of cost competitive fuels. MEK and BDO have both been shown to have excellent potential for conversion to sustainable aviation fuel (SAF) or SAF precursors.<sup>20, 23</sup>

However, challenges remain regarding the isolation of BDO from the fermentation broth, which is essential for further upgrading. Distillation is the most traditional approach to isolate and purify simple fermentation products such as ethanol, but in the case of BDO, incurs significant energy penalties due to the high boiling point of BDO (177 °C) relative to water.<sup>24, 25</sup> The most recent Biochemical Design Case Update published by the National Renewable Energy Laboratory (NREL)<sup>26</sup> describes an approach using a vacuum evaporator to pre-concentrate the broth followed by two sequential distillation towers to separate and purify the BDO from the water and residual solids to give approximately 92 % isolated yield. It is noted that this is a highly energy-intensive approach which will impact the overall cost of a commercial product and impact the carbon intensity of any BDO related process. Several other methods reported include liquid-liquid extraction<sup>27</sup>, pervaporation (membrane separation)<sup>28-30</sup>, anionic extraction<sup>31</sup> and sugaring-out extraction.<sup>32</sup> In addition to these, acetalization of 1,3-propanediol using concentrated H<sub>2</sub>SO<sub>4</sub> has been presented<sup>33</sup> and recent reports also suggested butanol-based extraction-assisted distillation for purification of 2,3-BDO.<sup>34-36</sup> However, these methods are hampered by inherent limitations and drawbacks; such as membrane fouling caused by other broth components, the use of a large excess of solvent, and low 2,3-BDO isolated yields.<sup>37</sup> Reactive extraction methods possess several advantages over distillation including large throughput and low energy consumption.<sup>38, 39</sup> However earlier reports of reactive extraction methodology for isolation of 2,3-BDO use strongly acidic environments that are corrosive and would require advanced alloys or coatings in plant equipment which may prove costly.

We have previously investigated the conversion of BDO into dioxolanes as candidates for compression ignition engine fuels (i.e., diesel).<sup>40, 41</sup> These were synthesized in a simple, solvent

free method through direct combination of a slight excess of BDO with an aldehyde using a solid acid catalyst (Amberlyst-15) to give the substituted 1,3-dioxolanes in near quantitative yield (Figure 1). A remarkable feature of this reaction was that while BDO and the aldehyde were miscible with one another, the dioxolane phase separated from this reaction mixture and was readily isolable by careful decantation of the upper layer as a pure product. These molecules exhibited excellent characteristics for diesel fuels with low water miscibility (< 40 mg/L water in each dioxolane we tested in Table S1).<sup>42</sup> Due to the measured dioxolane water immiscibility and the known water solubility of BDO and aldehydes, we were intrigued to assess the potential for dioxolane formation in aqueous solutions of BDO and whether this would also give good yields of dioxolane that would phase separate.



**Figure 1.** General reaction scheme for the direct conversion of aldehydes and 2,3-butanediol to synthesize dioxolanes.<sup>43</sup>

## Materials and Methods

### General

All the chemicals and solvents used in this study were purchased from commercial sources and used as received unless otherwise specified. 2,3-Butanediol (2,3-BDO) and aldehydes (butyraldehyde, 2-ethylbutyraldehyde, hexanaldehyde, 2-ethylhexandaldehyde, and octanal) were

purchased from Sigma-Aldrich. Aluminum oxide ( $\text{Al}_2\text{O}_3$ ) and aluminum phosphate ( $\text{AlPO}_4$ ) were purchased from Sigma-Aldrich, and ZSM-5 with Si/Al: 80 was purchased from Zeolyst. 2,3-BDO fermentation broths were obtained from National Renewable Energy Laboratory, NREL (Colorado, USA). Fermentation hydrolysate broth was received (2,3-BDO conc. 79.1 g/L).  $^1\text{H}$  NMR spectra for quantitative analysis were collected at room temperature on a Bruker AV400 MHz spectrometer. Chemical shifts were referenced to the residual solvent signal. Agilent 7890 GC system equipped with an Agilent 5975 mass selective detector (MSD), a flame ionization detector (FID) and a PolyArc system was used for GC-MS analysis.

### **BDO Separation Experiments:**

**General Small Scale BDO Conversion to Dioxolanes:** To a 20 mL scintillation vial containing ~1 mL of BDO solution (aqueous BDO solution, broth mimic or fermentation broth), 10 wt% acid catalyst (based on amount of aldehyde used) was added. To this mixture 5 equivalents of aldehyde was added dropwise and the reaction mixture was stirred (400 rpm) at 40°C for 5 hours. THF was added to the reaction mixture to help form a single phase solution and subsequently filtered to remove the catalyst using a filter Pasteur pipet. The filtered solution was diluted to 10 mL (in a volumetric flask) using THF. Percent conversion was calculated by GC-MS analysis using a normalized area ratio of BDO and dioxolane peaks. Note – Since each Nafion bead weigh roughly 40 mg and based on calculations (10 wt% of butyraldehyde), 1.6 mL of aq. BDO (70 g/L) or broth was used for reaction with Nafion as catalyst. This methodology was used to perform optimizations to study the effect of different catalysts, reaction temperatures and number of equivalents of selected aldehyde on the formation of dioxolane. Later, catalyst recycling experiments were also performed to analyze the efficiency of the catalyst under optimized conditions using this method.

**General Large Scale Experiment and Isolated Yield Calculations:** To a 100 mL round bottom flask containing 50 mL of pure sugar/hydrolysate broth,<sup>44</sup> 10 wt% Nafion (based on the amount of butyraldehyde used) was added. To this mixture, 5 equivalents of butyraldehyde were added dropwise and the reaction mixture was stirred (400 rpm) at 40 °C (used an oil bath) until reaction completion was confirmed by GC-MS analysis. The phase separated (i.e. top) layer was isolated using a pipet. The amount of mixture isolated (dioxolane and excess butyraldehyde) was weighed and yield calculated based on NMR integrations. The integration ratio of the C<sub>2</sub>-methylene proton of butyraldehyde (excess) and C<sub>2</sub>-methylene signal of the dioxolane formed were used for the isolated yield calculations. Dioxolane conversion and product carbon yield were calculated by the following equations:

$$\text{Dioxolane conversion (\%)} = \frac{\text{mole of dioxolane consumed}}{\text{mole of dioxolane fed}} \times 100$$

$$\text{Product carbon yield (\%)} = \frac{\text{carbon mole of product produced}}{\text{carbon mole of dioxolane fed}} \times 100$$

### **BDO recovery experiments**

**BDO Recovery via Deprotection:** To a 20 mL scintillation vial containing 100 mg of dioxolane (obtained from the separation experiments) and 4 mL of solvent (THF:Water = 3:1), 30 wt% Nafion-NR50 catalyst was added. The reaction mixture was stirred at 40°C for 3 and 24 hours, respectively. After the reaction, the filtered solution was analyzed by GC-MS and the conversion was calculated by GC-MS analysis.

**BDO Recovery via Trans-acetalization (methanolysis):** To a 20 mL scintillation vial containing 200 mg – 10 g of dioxolane (obtained from the separation experiments) and methanol solvent, 20

wt% Nafion catalyst was added. The reaction mixture was stirred at 40 °C for 6 hours. 2,3-BDO was recovered by distilling-off butyraldehyde dimethyl acetal formed in the reaction which matched  $^1\text{H}$  and  $^{13}\text{C}$  NMR and GC-MS with commercial 2,-3-BDO samples with no observable impurities.

**Conversion of Dioxolane to MEK and Butraldehyde Recovery:** Cleavage of the acetal (dioxolane) over an acid catalyst(s) was conducted in a plug flow reactor at atmospheric pressure and at  $1\text{h}^{-1}$  weight hourly space velocity (WHSV) over three different solid acid catalysts. The catalyst testing was conducted on a downflow reactor arrangement. The catalyst of interest was placed in the middle of the reactor tube in an isothermal zone and heated using a band heater to the desired reaction temperature. Dioxolane (using an HPLC pump) and carrier gas nitrogen ( $\text{N}_2$ ) was fed from the top of the reactor. The liquid product samples were collected at the bottom of the reactor in a cold trap. The products were speciated via gas chromatography-mass spectroscopy (GC-MS) and quantified with a flame-ionization detector (FID) using internal/external standards. The non-condensable gases from the cold trap passed through a flow meter (DryCal) and their composition was analyzed in gas chromatography-thermal conductivity detector (GC-TCD). The results reported in this work were based on the liquid sample collected over 24 hours.

## Results and Discussion

We screened the reactivity of five different aldehydes by reacting them (1.5 molar equivalents relative to BDO) with 1 mL of an aqueous solution of BDO (70 g/L) and an Amberlyst-15 catalyst (10 wt% relative to aldehyde) at room temperature or 40 °C for 5 hours. The reaction mixture was then made homogenous by adding tetrahydrofuran (THF) and filtering to remove the catalyst. The

filtered solution was diluted to 10 mL in a volumetric flask using additional THF. Percent conversion was calculated by GC-FID-PolyArc-MS analysis using a normalized area ratio of BDO and dioxolane peaks. The maximum conversion to dioxolane (80 %) was achieved with butyraldehyde at 40 °C. We followed this with reaction optimization based on acid catalyst, temperature, BDO:butyraldehyde ratio and concluded that 10 wt% Nafion at 40 °C for 4 hours in a 1:5 BDO:butyraldehyde ratio gave near complete conversion of BDO to the dioxolane (See SI for details). Amberlyst-15 (used in our original work) and Nafion had similar performance but due to the increased mechanical strength of the Nafion beads in stirred batch reactors, this was selected for further studies.<sup>45</sup> At temperatures above 55 °C conversion decreased due to the shift in reversible equilibrium. The optimized reaction conditions were used to perform 10 sequential reactions with the same Nafion catalyst bead with > 95% conversion maintained for each reaction and no observable loss in activity. To further probe the efficiency of this approach, we performed the reaction under these conditions at larger scale to determine isolable yield (50 mL, 70 g/L BDO solution, 2.5g BDO). Dioxolane phase separation was observed upon reaction completion and no detectable BDO was observed in the aqueous layer indicating complete BDO conversion. The phase separated layer was removed and analyzed by NMR spectroscopy and determined to be a mixture of dioxolane and excess, unreacted butyraldehyde. Based on the integration ratio of the C<sub>2</sub>-methylene proton of butyraldehyde and C<sub>2</sub>-methylene signal of the dioxolane, the upper layer contained 4:1 ratio of dioxolane:aldehyde with complete conversion of the BDO.

We then increased the reaction complexity by preparing a fermentation broth mimic (50 mL, 79 g/L BDO solution, 3.95 g BDO), replicating the composition of real hydrolysate fermentation broth (Table 1). Using identical reaction conditions, BDO in the broth mimic was completely converted to dioxolane that phase separated into an organic layer with approximately 4:1 ratio of



dioxolane:aldehyde. To identify any additional products derived from components other than BDO present in the product mixture we individually assessed the reactivity of the individual broth with butyraldehyde under optimized conditions. No reaction was observed with these binary combinations and no product formation was observed except for with glycerol. However, the product was hydrophilic enough to not phase separate and this was not observed in the organic layer with the dioxolane.

**Table 1.** Composition of 2,3-BDO hydrolysate fermentation broth used in this study.

Compound	Hydrolysate broth (g/L)
2,3-BDO	79.1
Glucose	1.4
Xylose	2.0
Arabinose	6.0
Acetoin	3.3
Glycerol	5.1
Xylitol	1.0
Lactic acid	2.0
Ethanol	0.8
Acetic acid	1.5

Moving to real fermentation broth produced at NREL from hydrolysate, initially proved challenging with low conversion observed for both broth samples. ICP-MS was performed on the hydrolysate broth (Table 2) which showed the presence of four metal elements, which could potentially bind to an acidic resin surface, resulting in the deactivation of Nafion for our reaction. We confirmed this by stirring hydrolysate broth with the catalyst, and analyzing the metal distributions in the post-treated hydrolysate broth. The ICP-MS results showed a 14-30 % and 83-99 % decrease in metal ions in the broth after Nafion and Amberlyst-15 treatment, respectively,

indicating the metal ion binding with both resin catalysts. This required us to remove all metal ions by treating the hydrolysate broth with an ion-exchange resin (Dowex 50WX8, 100-200 mesh) column without changing the BDO concentration (confirmed by ICP-MS results in Table 2).

**Table 2.** Metal distribution in hydrolysate broth before and after treatment characterized by ICP-MS.

<b>Sample/Metals (ppm)</b>	<b>K</b>	<b>Na</b>	<b>Ca</b>	<b>Mg</b>	<b>Fe</b>	<b>Al</b>
<b>BDO broth</b>	3357	1905	141	83	ND	ND
<b>BDO broth after Nafion treatment<sup>a</sup></b>	2350	1588	87	71	ND	ND
<b>BDO broth after Amberlyst treatment<sup>a</sup></b>	252	326	4	1	ND	ND
<b>BDO broth after Dowex treatment</b>	ND	ND	ND	ND	ND	ND

<sup>a</sup>stirring the mixture of Nafion NR50 or Amberlyst-15 (same catalyst ratio as in real reaction) and hydrolysate broth overnight at room temperature. ND = Not Detectable

With the metal-free hydrolysate BDO broth, we reassessed the activity and recyclability of Nafion under optimized conditions on small scale (1 mL). BDO can be completely converted over 10 sequential batch reactions using the same catalyst with a higher than 85% yield of dioxolane during the first 7 cycles decreased to 80% after 10 cycles (Figure S4), which could be caused by other unidentified impurities in the actual broth.

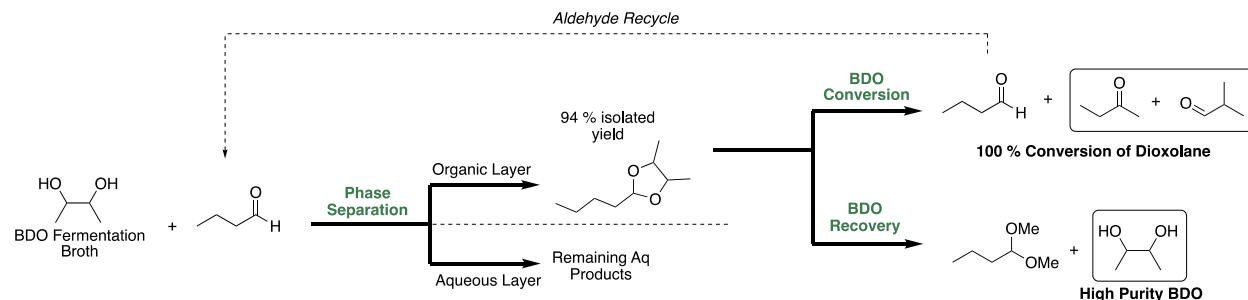
We then tested the Nafion activity on a larger scale with metal-free hydrolysate broth. A BDO separation experiment was carried out using 45 mL of metal-free hydrolysate broth under optimized conditions (5 equiv butyraldehyde and 10 wt% Nafion at 40 °C for 5 h). Dioxolane phase separation was observed upon reaction completion and 4.6% of the original BDO concentration was identified in the aqueous layer based on HPLC analysis with 95.4 % converted

to dioxolane (Figure S11). The phase separated layer was isolated and analyzed by NMR spectroscopy. Based on NMR analysis, nearly 4:1 ratio of dioxolane:butraldehyde was observed in the organic layer.

These results demonstrate a direct one step method to produce a promising fully bio-derived compression ignition fuel blendstock directly from fermentation broth. Butyraldehyde can be synthesized from the coupling of two bio-ethanol derived acetaldehyde molecules via crotonaldehyde or from the dehydrogenation of bio-butanol.<sup>43</sup> However, some value-added chemicals and demonstrated routes to SAF require high purity BDO. To address this application, we aimed to recover BDO from the dioxolane giving the opportunity to recycle the butyraldehyde. Hydrolysis or deprotection of an acetal is a well-known reaction.<sup>46, 47</sup> There are several reports of using heterogenous catalysts for these reactions, mainly due to their advantages with respect to the ease of recycling the catalyst during work-up.<sup>48-51</sup> Several reaction conditions were examined for recovery of BDO and results from these deprotection experiments are summarized in Table S3. Using Nafion (30 wt%) as a catalyst with dioxolane (100 mg) in aqueous THF resulted in nearly 70% conversion to BDO in the deprotection of the dioxolane. Methanolysis (trans-acetalization) was attempted on a small scale (200 mg) with nearly 90-95 % conversion and 70 % isolated yield of BDO using Nafion (20 wt%). On scale-up to 10g of dioxolane, the isolated yield increased to approximately 90% of very high purity BDO (> 99 %, based on NMR and GC). The methanolysis approach is attractive due to the fact that both methanol and dimethoxybutane are more volatile than BDO and would therefore be easily distilled to provide high purity BDO at scale.

Our second approach for the integrated process involves the conversion of biomass to MEK via the dioxolane intermediate. The main objective of this approach is to maximize the butyraldehyde

recycle, by avoiding its participation in the condensation reaction and simultaneously generating MEK and its derivatives for fuels generation. The cleavage of dioxolane was studied over an acid catalyst to identify the viability of this approach. The reaction scheme for dioxolane cleavage is shown in Scheme 1.

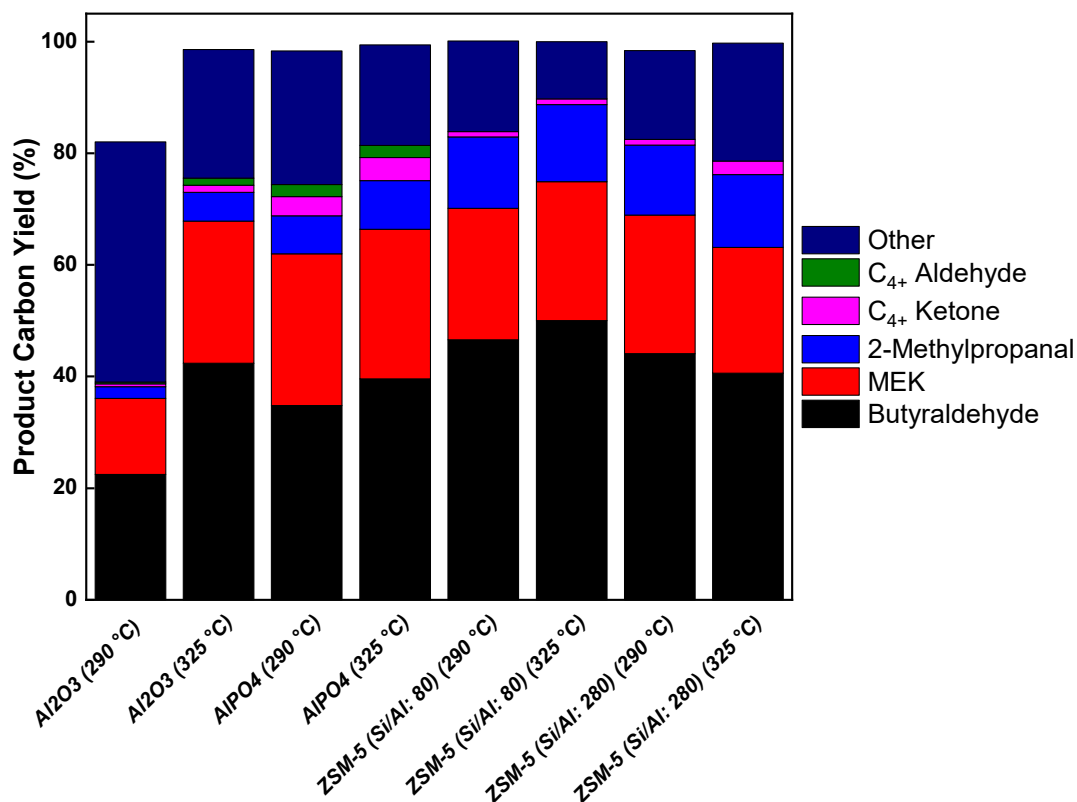


**Scheme 1.** Reaction scheme showing the dioxolane produced from 2,3-BDO broth can be used directly in a catalytic process as a BDO synthon to produce methyl ethyl ketone (MEK) and recover the aldehyde, as well as be converted to highly pure BDO through trans-acetalization.

Cleavage of the acetal over acid catalyst(s) was conducted in a plug flow reactor at atmospheric pressure and at  $1\text{h}^{-1}$  weight hourly space velocity (WHSV) over three different solid acid catalysts. The results from the experimental work is shown in Figure 2. The catalysts tested for this initial study were 1) aluminum oxide ( $\text{Al}_2\text{O}_3$ ), 2) aluminum phosphate ( $\text{AlPO}_4$ ), 3) ZSM-5 with Si/Al:80, and 4) 3) ZSM-5 with Si/Al:280. Each was examined at  $290\text{ }^\circ\text{C}$  and  $325\text{ }^\circ\text{C}$ .

Conversions of dioxolane was different for all three catalysts at  $290\text{ }^\circ\text{C}$  ( $\text{ZSM-5} > \text{AlPO}_4 > \text{Al}_2\text{O}_3$ ) but at  $325\text{ }^\circ\text{C}$ , all three catalysts performed at conversion levels  $> 95\%$ . Among the catalysts tested, ZSM-5 shows the best selectivity for butyraldehyde (close to a stoichiometric value around  $50\%$ ) and  $\text{AlPO}_4$  has the lowest selectivity for butyraldehyde. The lower selectivity of butyraldehyde is

due to the promotion of the self-aldol condensation of butyraldehyde and the cross-aldol condensation between the butyraldehyde and MEK (or 2-methylpropanal (isobutyraldehyde)).



**Figure 2.** Dioxolane conversion to butyraldehyde and methyl ethyl ketone at various solid acid catalyst. Atmospheric pressure,  $1\text{h}^{-1}$  weight hourly space velocity.

Other than butyraldehyde, both MEK and 2-methylpropanal were observed as the primary products from dioxalane conversion over all three acid catalysts, with ZSM-5 exhibiting the highest yields to 2-methylpropanal. The total selectivity to MEK and 2-methylpropanal across all the catalysts was around 40%, slightly less than what would be expected from the stoichiometric cleavage of dioxolane (50%). This observed difference can be attributed to the formation of C<sub>8+</sub> compounds from the cross-condensation reaction. Given that these larger compounds are also

suitable for feeding into downstream fuel synthesis steps along with MEK, the formation of these condensation products do not negatively impact the overall carbon efficiency of BDO conversion to fuels, which should be close to stoichiometric levels based on this approach.

In summary, a reactive extraction (acetalization) approach was developed to convert BDO to dioxolane directly in fermentation broth. The dioxolane phase separates to give a 4:1 mixture of dioxolane:butraldehyde with approximately 95% conversion and extraction of the BDO. The dioxolane can either be used directly as compression ignition fuel, used to yield a very high purity BDO via methanolysis or used as a BDO synthon. The economic feasibility and greenhouse gas (GHG) reduction potential of this approach will depend on a number of factors including source of biomass input, availability of bio-derived aldehyde and overall carbon yield into the final product. We are actively pursuing systematic improvements that will address these key barriers to commercialization. This provides an opportunity to implement a novel separation approach to further advance the bioeconomy and avoid traditional energy intensive distillations. This approach will aid in the commercialization of BDO as a new bioderived building block suitable for decarbonizing the transportation sector and in particular low carbon SAF.

## ASSOCIATED CONTENT

**Supporting Information.** Experimental details and analytical details are shown in the SI.

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### **Author Contributions**

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