PRODUCTION OF NEO ACIDS FROM BIOMASS-DERIVED MONOMERS

by

Erha Gelania Andini

A thesis submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Master of Chemical Engineering

Winter 2024

© 2024 Erha Andini All Rights Reserved

PRODUCTION OF NEO ACIDS FROM BIOMASS-DERIVED MONOMERS

by

Erha Gelania Andini

Approved:

Dionisios Vlachos, Ph.D Professor in charge of thesis on behalf of the Advisory Committee

Approved:

Millicent Sullivan, Ph.D. Chair of the Department of Chemical and Biomolecular Engineering

Approved:

Levi T. Thompson, Ph.D. Dean of the College of Engineering

Approved:

Louis F. Rossi, Ph.D. Vice Provost for Graduate and Professional Education and Dean of the Graduate College

ACKNOWLEDGMENTS

First and foremost, I would like to express my deepest gratitude to my advisor, Professor Dionisios G. Vlachos. Thank you for your guidance, encouragement, feedback, patient and valuable mentorship during my research.

This work was supported as part of the Catalysis Center for Energy Innovation, an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, and Office of Basic Energy Sciences under award number DE-SC0001004.

Thank you to every member of the Vlachos lab for their support and assistance during my graduate career. Special thanks to Dr. Sunitha Sadula who worked with me on this project.

Finally, sincere appreciation to my parents and family members, who constantly supported me with their unconditional love.

TABLE OF CONTENTS

LIST OF TABLES	vi
LIST OF FIGURES	.vii
ABSTRACT	viii

Chapter

1	INTRODUCTION
2	MATERIALS AND METHODS
	Chemicals and materials
	Materials Pretreatment
	Reaction procedures
	Hydroxyalkylation/alkylation (HAA)6
	Hydrodeoxygenation
	Derivatization technique
	Analysis of products and catalyst 7
	Computational methods
	Multi-parameter optimization using NEXTorch 8
	Machine learning analysis
3	RESULTS AND DISCUSSIONS
	Hydroxyalkylation/alkylation10
	Catalyst screening and product yield optimization
	katonas 12
	IIAA astalast sassalahiitta
	HAA catalyst recyclability
	Hydrodeoxygenation16
	Catalyst screening16
	Solvent screening
	Reaction parameter optimization19
4	CONCLUSIONS
DEEE	PENCES 22
КЕГЕ	KENCES

Appendix

А	TABLES AND FIGURES	27
В	PERMISSIONS FOR REPRINT	44

LIST OF TABLES

Table 1	HAA reaction between different 2-alkylfurans and keto acid of varying molecular sizes	14
Table 2	Catalyst screening for the HDO of FNA and FNA RO	17
Table A.1	Summary of catalyst screening	28
Table A.2	Initial HAA reaction rate data	30
Table A.3	Properties of commercial solid acid catalysts	30
Table A.4	Summary of multi-parameter optimization using NEXTorch	33
Table A.5	Detailed experimental results of HAA reaction between different 2- alkylfurans and keto acid of varying molecular sizes	38
Table A.6	The effect of catalysts on product distribution	39
Table A.7	Esterification of FNA with alcohol (methanol) making FNE	42

LIST OF FIGURES

Figure 1	Approaches to synthesize branched monocarboxylic acids
Figure 2	Reaction products from the HAA reaction of 2-pentylfuran and levulinic acid and catalysts screening results
Figure 3	Recyclability of Aquivion PW79S in the HAA reaction of 2- pentylfuran and levulinic acid
Figure 4	The effect of solvent on the HDO reaction. C23-NA is neo acid with 23 carbon atoms
Figure 5	Effect of reaction parameters on product distribution for the HDO reaction
Figure A.1	The synthesis of furan, 2-methylfuran, 2-alkylfuran, levulinic acid, and pyruvic acid
Figure A.2	Reaction mechanism for the condensation of 2-pentylfuran with levulinic acid
Figure A.3	GC chromatogram overlay
Figure A.4	Effect of geometry
Figure A.5	Scree plot of PCA analysis
Figure A.6	Multi-parameter optimization using NEXTorch for the HAA reaction 36
Figure A.7	FT-IR spectra of fresh and used Aquivion PW79S catalysts
Figure A.8	GC overlay for the HDO product mixture obtained with and without a catalyst
Figure A.9	LCMS of HDO product solution
Figure A.10	Effect of water addition and used catalyst removal
Figure A.11	Time-dependent study of FNE ring-opening

ABSTRACT

Neo acids are highly branched carboxylic acids currently produced from fossil fuels. In this work, we produce renewable neo acids from lignocellulosic biomassderived furan and keto acids *via* C–C coupling through hydroxyalkylation/alkylation (HAA), followed by ring-opening of furans through hydrodeoxygenation (HDO). We show effective C–C coupling over acid catalysts. Catalyst screening and multiparameter optimization using machine learning optimize the yield and elucidate the correlation between variables and outcomes. We demonstrate selective furan ringopening without affecting the carboxylic acid to make neo acids using a co-catalyst involving Pd supported on carbon and metal triflate.

Chapter 1

INTRODUCTION

The global population growth and improved quality of life have increased the demand for fuels, chemicals, and other products.^{1,2} The increased agriculture and industrial manufacturing depend on fossil fuels. The associated environmental concerns demand renewable and sustainable alternatives. Lignocellulosic biomass, including forest wood, municipal solid waste, energy crops, and agriculture residue, is an abundant, renewable, non-edible promising alternative to fossil fuels. Recent advancements in conversion technologies of lignocellulosic biomass create unique opportunities to make valuable fuels and chemicals, such as lubricants, plastics, rubber, and detergents.^{3–7}

Neo acids are highly branched *tert*-monocarboxylic acids commercially produced from fossil fuels. The high steric hindrance due to their structure imparts excellent thermal and hydrolytic stability, and resistance to chemicals and oxidative compounds. Their low pour point allows for easy transportation, storage, and handling.^{8,9} Depending on the chemistry applied to the carboxylic functional group (reduction, dehydration, esterification, etc.), derivatives with diverse applications can be obtained, including polymers, adhesives, lubricants, agrochemicals, paints, coatings, and personal care products.^{4,7,10–15} Neo acids are commercially manufactured from petroleum-derived olefins (isobutene and mixed nonenes) through the Koch synthesis (Figure 1A&B),^{8,16,17} such as neopentanoic acid and neodecanoic acid (ExxonMobil) and versatic acid (Hexion). However, the process involves harsh reaction conditions,

such as high temperatures and pressures and strong acids, *e.g.*, H₂SO₄, HNO₃, H₃PO₄, HF, and toxic substances, which cause environmental concerns. Additionally, multistep purifications are needed to separate dimeric and trimeric isobutene by-products. Thus, there remains a need for sustainable and environmentally friendly alternatives to produce neo acids from renewable resources, such as biomass.

Research into the chemical synthesis of branched carboxylic acids from biomass is still rare, with much attention on naturally occurring ones and microbial fermentation. Dembitsky presented a review of naturally occurring neo acids covering their identification in plants, algae, fungi, marine invertebrates, and microorganisms and isolation methods.⁹ However, these processes are not economical and suffer from scalability issues. Microbial fermentation has been explored to produce branched carboxylic acids derived from biomass,^{18–20} but the process is challenged by long fermentation time, selectivity, and enzyme inactivation. Li *et al.* described the chemical synthesis of medium-chain carboxylic acids from cellulose-derived platform chemicals (Figure 1C).²¹ However, the process uses a corrosive solvent, the products are straight-chain and iso carboxylic acids, and the chain length cannot be tailored. To the best of our knowledge, no reports on the catalytic synthesis of highly branched *tert*-monocarboxylic acids from biomass exist.



Figure 1 Approaches to synthesize branched monocarboxylic acids. Industrial route to produce A) neopentanoic acid and B) neodecanoic acid. C) Chemical synthesis of medium-chain carboxylic acids from biomass. D) Our approach to renewable neo acids by hydroxyalkylation/alkylation (HAA) of 2-alkylfurans with levulinic acid (LA) or pyruvic acid (PA) followed by hydrodeoxygenation (HDO).

Here, we report a strategy to synthesize renewable neo acids with tailored molecular architecture from biomass-derived 2-alkylfuran and keto acids, *e.g.*, levulinic acid (LA) or pyruvic acid (PA), through C-C coupling of furans via hydroxyalkylation/alkylation (HAA) using a Brønsted acid catalyst followed by furan ring-opening (RO) via hydrodeoxygenation (HDO) using metal triflate and Pd/C (Figure 1D). 2-alkylfuran with varying chain lengths can be produced through dehydration and HDO of biomass-derived C₅ sugars or furan acylation with valeric acid or valeric anhydride followed by HDO^{7,22,23}. LA can be synthesized via dehydration of

fructose followed by rehydration²⁴, and PA can be obtained via fermentation of glucose²⁵ (Figure A.1). While HAA chemistry has been reported to increase the carbon number of biomass-derived platform molecules and HDO chemistry has been reported for the RO of furan and other aromatic functionalities to make jet fuels, diesel, and lubricants from biomass,^{26–33} the synthesis of highly branched carboxylic acids with tailored molecular architecture has not yet been reported. Wang *et al.* reported the HAA reaction between 2-methylfuran and angelica lactone (LA self-condensed product) producing renewable diesel with low yield (4.8%).²⁹ In our work, the HAA reaction successfully converts the reactants into furan-containing neo acids (FNA) and its ring opening (FNA RO) over Brønsted acid catalysts with more than 90% yield. Upon catalyst and solvent screening, and optimization of the HDO step gives a 40% yield of the desired neo acid (C₂₃-NA) with 15% of iso acid (C₁₄-IA), a commercially valuable cracked product.

Chapter 2

MATERIALS AND METHODS

Chemicals and materials

Aquivion® PW79S (coarse powder, Brunauer-Emmett-Teller (BET) surface area <1 m²/g, and 1.26 mmol H⁺/g), Aquivion® PW98 (coarse powder, BET surface area $<1 \text{ m}^2/\text{g}$, and 1.0 mmol H⁺/g), phosphotungstic acid hydrate (BET surface area <1 m^2/g and 1.04 mmol H⁺/g), phosphomolybdic acid hydrate (BET surface area 1-5 m²/g and 1.5 mmol H⁺/g), amorphous silica alumina (ASA; catalyst support grade 135; 12 wt % Al₂O₃; >90% AS-100 mesh; pore size, 5.4 nm; BET surface area, 569 m2/g; and 0.34 mmol H+/g), 2-methylfuran (99%), 2-pentylfuran (\geq 98.0%), 2-ethylfuran (\geq 99.0%), levulinic acid (98%), pyruvic acid (98%), eicosane (99%), ethyl acetate (99.8%), acetic acid (≥99.7%), methanesulfonic acid (≥99.0%), p-toluenesulfonic acid monohydrate (≥98.5%), triflic acid (≥99.0%), Eu(OTf)₃ (98%), La(OTf)₃ (99%), Nd(OTf)₃ (98%), Sc(OTf)₃ (99%), Cu(OTf)₂ (99%), Zn(OTf)₂ (99%), Ag(OTf) (≥98%), Sm(OTf)₃ (98%), Pd/C (10 wt % Pd loading), Pt/C (10 wt % Pt loading), pyridine (99.8%), and N,O-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) (≥99.0%) were purchased from Sigma-Aldrich. Cyclohexane (99.9%) and methanol (≥99.9%) was purchased from Fisher Chemical. 2-Propylfuran (>98%) and 2-butylfuran (>98%) were purchased from Tokyo Chemical Industry Co. Ltd. HY (CBV720; Si/Al = 15; pore size, ~0.7 nm; BET surface area 780 m²/g; and 0.31 mmol H⁺/g) was purchased from Zeolyst. H₂SO₄ (5 M) was purchased from Fluka. Ru/C (10 wt % Ru loading) was purchased from Riogen. $Hf(OTf)_4$, $Al(OTf)_3$ (99%), $Ce(OTf)_4$ (98%), $Sn(OTf)_2$ (97%), and 2-heptylfuran (97%) were purchased from Alfa Aesar.

Materials Pretreatment

2-Alkylfurans (2-methylfuran, 2-ethylfuran, 2-propylfuran, 2-butylfruan, 2pentylfuran, 2-hexylfuran and 2-heptylfuran) were purified by vacuum distillation before use.

Reaction procedures

Hydroxyalkylation/alkylation (HAA)

In a typical reaction, 20 mmol (2.76 g) 2-alkylfuran, 10 mmol (1.16 g) levulinic acid or 10 mmol (0.88 g) pyruvic acid, and a calculated amount of catalyst were mixed in a 50 mL round-bottom flask without any solvent. The flask was placed in a preheated oil bath and magnetically stirred at 800 rpm. The reaction was run at the desired temperature for a specified reaction period. After the reaction, the solution was diluted using 10 ml of cyclohexane and 5 mL ethyl acetate solvents. Ethyl acetate was used to solubilize unreacted levulinic acid. Eicosane (C_{20}) was added as an internal standard, and the catalyst was separated from the solution by syringe filtration.

Hydrodeoxygenation

HDO of FNA over metal triflate was performed in a 50-mL Parr reactor (4790 pressure vessel, Parr Instrument Company) with an inserted glass liner and a magnetic stirrer. First, 1 mmol (0.37 g) of FNA, 6 mol% (0.029 g) Al(OTf)₃, 2 mol% (0.021 g) of 10 wt% Pd/C, and solvent (10 mL of cyclohexane) were added to the reactor, and the reactor was sealed with the reactor head equipped with a thermocouple, a rupture disk,

a pressure gauge, and a gas release valve. The reactor was purged with 1 MPa N_2 five times and followed by 1 MPa H_2 five times, and finally pressurized to the desired H_2 pressure. The reaction mixture was heated to the desired temperature with continuous stirring at 750 rpm. The heating time to reach the set temperature was about 20 min. Once the desired temperature was reached, the mixture was run for a specified reaction period. Upon completion, the reactor was immediately transferred to an ice bath, cooled to room temperature, and H_2 was released. The reaction solution was diluted using 5 mL of ethyl acetate with a small amount of decane (C₁₀) as an internal standard, and the catalyst was separated from the solution by filtration.

Derivatization technique

Silylation, a derivatization technique, was implemented to improve the chromatographic behavior of the polar neo acid compounds and intermediates. Silylation works by selectively replacing the active hydrogens on the compound with an alkylsilyl group, resulting in less polar and more volatile compounds and better separation in gas chromatography (GC).51 In a typical reaction, 100 μ L product, 900 μ L solvent, 250 μ L pyridine, and 250 μ L BSTFA were mixed in a GC vial. Then, the solution was heated on a hot plate at 65°C for 20 minutes.

Analysis of products and catalyst

The products were analyzed using a gas chromatograph (Agilent 7890A) equipped with an HP-1 column and a flame ionization detector (FID). The products were identified by a GC (Agilent 7890B) mass spectrometer (MS, Agilent 5977A with a triple-axis detector) equipped with a DB-5 column, high-resolution MS with liquid injection field desorption ionization (LIFDI), ¹H nuclear magnetic resonance (NMR),

and ¹³C NMR (Bruker AV400, CDCl₃ solvent). Fourier transform infrared (FTIR) data was collected with a Thermo Fisher FTIR/ATR by scanning the sample from 400 to 4000 nm.

The conversion and yield of all products were calculated on a carbon basis using the following equations:

Conversion (%) =
$$\frac{\text{Moles of carbon converted}}{\text{Moles of carbon in initial reactant}} \times 100\%$$
 (1)

$$Yield (\%) = \frac{Moles of carbon product}{Moles of carbon in initial reactant} \times 100\%$$
(2)

Computational methods

Multi-parameter optimization using NEXTorch

To maximize the reactants' conversion and product yield, a multi-parameter optimization was conducted using NEXTorch, a recently developed active learningdriven optimization toolkit in our group.⁵² Reaction parameters, including temperature, time, molar ratio, and catalyst loading, influence the FNA selectivity. Many studies have reported optimization studies of HAA chemistry by changing one parameter at a time.^{30,35,37,53} The one at the time approach prevents us from optimizing FNA yield by changing all parameters simultaneously and understanding correlations between parameters. The traditional factorial design of experiments (DOE) has been implemented for a long time^{54,55} to optimize lab-scale production of fuels and chemicals from biomass.^{56–59} However, the typical traditional DOE is static. Therefore, implementing a method that captures interactions among parameters and minimizes the number of experiments is essential to further understand the chemistry. NEXTorch integrates design of experiments (DOE), Bayesian optimization, and surrogate modeling to optimize the function of interest, i.e., objective function.⁵² The initial DOE and subsequent sampling points were generated using pyKriging, an open-source kriging software in Python.

Machine learning analysis

Principal Component Analysis (PCA) was carried out using the Minitab software.

Chapter 3

RESULTS AND DISCUSSIONS

Hydroxyalkylation/alkylation

Catalyst screening and product yield optimization

Different homogeneous and heterogeneous acid catalysts were evaluated using 2-pentylfuran (2-PF) as the model compound and levulinic acid under the reaction conditions of our previous work³⁴ (Figure 2). The acid catalysts included H₂SO₄, CH₃SO₃H, and *p*-TSA, hetero-poly acids (phosphotungstic acid (PTA), phosphomolybdic acid (PMA), and perfluorinated sulfonic acid resins (Aquivion PW79S and Aquivion PW98), commercial HY, and silica-alumina at equivalent acid (H⁺) amounts. As shown in Figure 2A, all catalysts except HY zeolite and silica-alumina produced FNA as the main product and small fractions of other products via RO of the FNA (FNA RO) and self-condensation of 2-PF (SC-1, SC-2, SC-3, and SC-4) referred as PFSCs (Figure 2B). The conversions and yields are listed in Table A.1. Water, a byproduct of the condensation chemistry, likely facilitated the formation of FNA RO and PFSCs through acid-catalyzed hydrolysis and self-condensation, respectively. The mechanism of the HAA chemistry has been reported (Figure A.2).³⁴ The initial reaction rate data (Table A.2) at various temperatures was used to estimate the apparent activation energies (E_a). An E_a of 34.3 kJ mol⁻¹ was obtained. The performance was evaluated based on the combined yields of FNA and FNA RO, as FNA RO also produces neo acid upon HDO reaction. The catalytic performance follows the order of Aquivion PW79S > PTA > PMA > p-TSA > CH₃SO₃H > H₂SO₄ > Aquivion PW98 > HY. Silica-alumina shows no activity. Aquivion PW79S resulted in an overall FNA and FNA RO yield of 90% at a complete conversion of 2-PF and LA conversion of 82%.

Blank experiments of 2-PF and LA alone over Aquivion PW79S (Figure A.3) confirm no self-condensation of 2-PF or LA. Aquivion PW79S was selected for the remaining experiments reported below.

While homogeneous acids, such as H₂SO₄, CH₃SO₃H, and *p*-TSA, give good overall yield (Figure 2A), they are corrosive and difficult to separate and recycle.^{4,34-36} Amongst the heterogeneous catalysts, the overall yield of FNA and FNA RO can differ due to the catalyst's acid strength and density, surface area, and pore size (Table A.3).^{36,37} The high catalytic performance of Aquivion PW79S compared to the other acid catalysts can be attributed to its higher acid density, enabling higher accessibility of H⁺ for the tandem C–C coupling reaction.^{38,39} It is worth mentioning that the water by-product of HAA and the amphiphilic nature of perfluorinated sulfonic acid resin catalysts result in water clusters swelling the catalyst. Aquivion PW79S is more prone to swelling than Aquivion PW98 due to its higher acid density.^{40,41} This phenomenon limits reactant accessibility to the active sites. The formation of water channels can be mitigated simply by performing reactions in a round bottom flask under high stirring speed (Figure A.4).



Figure 2 Reaction products from the HAA reaction of 2-pentylfuran and levulinic acid and catalysts screening results. A) Proposed reaction network for the formation of condensation products. B) FNA and FNA RO yield over various acid catalysts. Reaction conditions: 20 mmol 2-pentylfuran (2-PF), 10 mmol levulinic acid (LA), 0.107 mmol H^+ catalyst, 65°C, 6 h, 800 rpm.

Optimization of the operating conditions using active learning (see Methods) led to an overall yield of 90% at complete conversion of 2-PF and 82% conversion of LA under 2-PF/LA molar ratio of 2, Aquivion PW79S loading of 0.107 mmol H⁺, a temperature of 65 °C, time of 6 h, and stirring speed of 800 rpm (Table A.4). Analysis of the data using principal component analysis (PCA) shows revealed correlations among parameters (Figure A.6).

Extending the HAA chemistry to different 2-alkylfurans and ketones

The optimal reaction conditions were applied to other 2-alkylfurans and keto acids to obtain neo-acid precursors of varying chain length (Table 1). Pyruvic acid on average produces 10% more neo-acid precursor than levulinic acid likely due to the closer distance of the keto group to the –COOH group, resulting in an increase in reactivity due to a stronger electron withdrawing impact by the –COOH group. High overall yields of C_{13} - C_{27} FNA and FNA RO (47% to 92%, depending on the molecular sizes) over Aquivion PW79S were obtained, except for Entry 1. The substantially lower combined yield of FNA and FNA RO, when R is a methyl group (2-MF), is due to the self-condensation of 2-MF. This is supported by the low conversion of levulinic acid (58%) even though almost all 2-MF is converted (Table A.5). A low total carbon balance (75%) was also obtained after accounting all the peaks on the GC spectra, suggesting the formation of high-molecular weight molecules not detected by GC/GC-MS. A low kinetic barrier for self-condensation is possible.⁴² Nonetheless, the data shows a promising route to synthesize neo-acid precursors with tunable structures.

Table 1. HAA reaction between different 2-alkylfurans and keto acid of varying molecular sizes. Reaction Conditions: 20 mmol 2-alkylfuran, (2-alkylfuran/keto acid) (mol/mol) = 2, 0.107 mmol H⁺ Aquivion PW79S, 6 h, 65°C, 800 rpm.

$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \end{array} \\ \end{array} \\ 2^{O} \\ \end{array} \\ \xrightarrow{2^{-} Alkylfuran} \end{array} + \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} $ \end{array} \\ \end{array} \\ \end{array} \end{array} \\ \end{array} \end{array} \\ \end{array} \end{array} \\ \end{array} } \\ \end{array} } \\ \end{array} } \\ \end{array} \\ \\ \end{array} } \\ \end{array} \\ \\ \end{array} } \\ } \\ \end{array} } \\ \end{array} } \\ \end{array} } \\ } \\ \end{array} } \\ } \\ \end{array} } \\ \end{array} } \\ \end{array} } \\ \end{array} } \\ } \\ \end{array} } \\									
Entry	Reag	ents	#C	Yield FNA + FNA RO	Total C Balance (%)				
·	R	Keto Acid		(%)	(70)				
1	Methyl	LA	C ₁₅	47	75				
2	Ethyl	LA	C ₁₇	77	94				
3	n-Propyl	LA	C19	87	102				
4	n-Butyl	LA	C ₂₁	75	87				
5	n-Pentyl	LA	C ₂₃	90	101				
6	n-Heptyl*	LA	C ₂₇	82	89				
7	Methyl	РА	C ₁₃	86	93				
8	Ethyl	PA	C ₁₅	87	90				
9	n-Propyl	PA	C ₁₇	92	95				
10	n-Butyl	PA	C19	90	92				
11	n-Pentyl	РА	C ₂₁	86	89				
12	n-Heptyl	РА	C ₂₅	79	84				

*Ten hours reaction time. #Carbon chain length



Figure 3 Recyclability of Aquivion PW79S in the HAA reaction of 2-pentylfuran and levulinic acid. Reaction conditions: 20 mmol 2-pentylfuran (2-PF), 10 mmol levulinic acid (LA), 0.107 mmol H^+ catalyst, 65°C, 6 h, 800 rpm.

For assessing catalyst recyclability, the liquid products were decanted out after each cycle. The catalyst was washed thrice with cyclohexane and ethyl acetate to remove surface-adsorbed unreacted reactants and products and then dried in a vacuum oven at 60 °C for 1 h before reuse in the next cycle. Figure 3 shows that the catalyst achieves similar conversions and yields in five consecutive cycles. The slight decrease in LA conversion and product yields among cycles can be attributed to slight deactivation, likely due to covering some of the catalyst sites by adsorbed products. This is supported by FT-IR results on the spent catalyst showing additional bands at 2800–3000 cm⁻¹ corresponding to C–H stretching (Figure A.7).

Hydrodeoxygenation

Catalyst screening

We adapted our previously furan ring-opening reaction conditions employed in the production of adipic acid^{43,44} and decanoic acid²¹. Initially, we implemented Gilkey *et al.* and Tran *et al.* catalytic systems due to their promising results in selectively opening the tetrahydrofuran (THF) ring without impacting the carboxylic acid groups in making adipic acid. Hydrogenation was performed on the HAA product solution containing FNA, FNA RO, PFSCs and unreacted LA (after catalyst filtering) over Pd/C to saturate the furan ring. The reaction conditions were selected from our previous work.⁴ The tetrahydrofuran-containing neo acid (THFNA) was successfully formed at nearly 95% yield but neo acid did not form in the ring opening step over Nafion and iodide salt (Table 2, entry 1). Ring opening of the hydrogenated product using [MIM(CH₂)₄SO₃H]I ionic liquid⁴⁴ did not form a neo acid (Table 2, entry 2). The difference in the activity of tetrahydrofuran-based in our work and the tetrahydrofuran-2,5-dicarboxylic acid (THFDCA) in the literature is the two carboxylic acid groups that withdraw electrons facilitating the ring opening. Their absence makes ring-opening chemistry more challenging.

The HDO reactions using metal triflates and Pd/C catalysts²¹ convert the HAA product solution into C₂₃-neo acid (C₂₃-NA). Here, Pd/C acts as a hydrogenation catalyst and metal triflate as the ring-opening catalyst. The HDO reaction also produced a cracked product, C₁₄-iso acid (C₁₄-IA). Nearly 30% of the total carbon was missing. The iso acids in the current process are commercially valuable, *e.g.*, the isostearic acid is used widely in additives, emollients, hydraulic fluids, and personal care emollients.⁴⁵ Given the promising preliminary results, other metal triflates were screened and found that the higher the effective charge density on the metal cation, the higher the selectivity toward C₂₃-NA (Table 2, entries 5 - 16).^{21,46} The highest yield was 37% C₂₃-NA and

 \sim 13% C₁₄-IA with Al(OTf)₃ and Pd/C co-catalyst. Although cerium and hafnium triflate have higher effective charge density than aluminum triflate, they yield lower neo acids. This could be due to their higher sensitivity to the water by-product compared to aluminum triflate.^{47,48}

R			+	он	
FN	IA (C ₂₃ -FNA) R = C ₅ H ₁₁	NA (C ₂₃ -NA)	IA (C ₁₄ -IA)		
F 4	Hydrogenation	D	Yi	eld (%)	
Entry	Catalyst	Promoter	C ₂₃ -NA	C ₁₄ -IA	
1 ^a	-	Nafion + LiI	-	-	
2 ^b	-		-	-	
		[MIM(CH ₂) ₄ SO ₃ H]I			
3	Ru	Al(OTf) ₃	_	_	
4	Pt	Al(OTf) ₃	21	11	
5	Pd	Al(OTf) ₃	37	13	
6	Pd	Hf(OTf)4	31	15	
7	Pd	Ce(OTf) ₄	20	1	
8	Pd	La(OTf) ₃	1	0	
9	Pd	Sm(OTf) ₃	0	2	
10	Pd	Eu(OTf) ₃	17	10	
11	Pd	Nd(OTf) ₃	1	12	
12	Pd	Sc(OTf) ₃	9	12	
13	Pd	Cu(OTf) ₂	14	9	
14	Pd	Sn(OTf) ₂	15	30	
15	Pd	Zn(OTf) ₂	1	9	

Table 1. Catalyst screening for the HDO of FNA and FNA RO.

Reaction conditions: Entries 3-16 correspond to 1 mmol FNA, 6 mol% M(OTf)_x, 2 mol% hydrogenation catalyst, 10 mL n-octane, 3 MPa H₂, 180°C, 1 h, 500 rpm. Conversion \geq 99% & total carbon balance \leq 70%. ^(a) Entry 1 for hydrogenation reaction: 0.5 g HAA solution, 0.03 g Pd/C, 10 mL cyclohexane, 60°C, 2 h, 6 MPa H₂, 500 rpm. Pd/C was reduced under H₂ (50 mL/min) at 200°C for 1 h; Deoxygenation reaction: 1 wt% THFNA, 0.3 M H⁺ Nafion, 0.3

Ag(OTf)

25

3

16

Pd

M lithium iodide (LiI), 15 mL propionic acid, 160°C under 500 psi H₂, 2 h. ^(b) Entry 2: hydrogenation reaction as in (a) followed by deoxygenation reaction: 0.165 g THFNA (0.165 g), 1.55 g [MIM(CH₂)₄SO₃H]I, 2 h, 3.5 MPa H₂, 180°C, and 500 rpm.

Solvent screening

Different organic solvents were screened (Figure 4). A solvent-free reaction is not practical as the HAA solution is highly viscous. We found that non-polar organic solvents yield higher C_{23} -NA due to the better solubility of reactants, intermediates, and products without reacting with the metal triflate.²¹ When a polar protic solvent, such as acetic acid, was used, esters and cracked products formed along with the neo acid. In polar aprotic solvents, such as ethyl acetate and THF, no reaction occurred likely due to deactivation of the metal triflate. According to Zhou *et al.*⁴⁷ and Keskiväli *et al.*⁴⁹, metal triflate with solvents bearing Lewis basic oxygen atoms ensued coordination between the metal center and the polar solvent, resulting in metal triflate deactivation. Mixtures of polar and non-polar organic solvents were explored to improve solvation of the substrates but no improvement in the C₂₃-NA yield.



Figure 4 The effect of solvent on the HDO reaction. C23-NA is neo acid with 23 carbon atoms. C14-IA is iso acid with 14 carbon atoms. Reaction conditions: 1 mmol FNA, 6 mol% Al(OTf)₃, 2 mol% Pd/C, 10 mL solvent, 3 MPa H₂, 180°C, 1 h, 500 rpm.

Reaction parameter optimization

To investigate the role of hydrogenation catalyst and metal triflate on the HDO chemistry, control experiments were conducted with Pd/C alone and metal triflate alone and results are presented in Table A.6. The GC chromatograms for each reaction are overlaid in Figure A.8. In the control reaction of Al(OTf)₃ alone, neither neo acid nor unreacted HAA products were observed, likely due to self-oligomerization of the starting materials facilitated by the metal triflate. This hypothesis is supported by the black color and turbid solution upon reaction (Figure A.8B) and high molecular weight species detected by LCMS (Figure A.9). Similarly, neither neo acid nor starting materials were observed over Pd/C alone. Instead, THFNA formed in quantitative yield (Figure A.87C), consistent with Pd's reported activity for furan ring-hydrogenation.²³ These control experiments confirm no self-condensation of the FNA and FNA RO being responsible for the missing carbon balance. These results also indicate that Pd/C and metal triflate are required to form neo acid.

The effect of varying catalyst molar ratio, hydrogen pressure, temperature, and time were also studied (Figure 5). We found that the HDO reaction required a suitable ratio of the hydrogenation catalyst (Pd/C) and metal triflate to form neo acid (Figure 5A). The yield of C₂₃-NA initially increased and then decreased with increasing the ratio of Al(OTf)₃. The same trend was observed with varying the Pd/C. We found that C₂₃-NA yield increases with increasing hydrogen pressure and plateaus above 3 MPa. The increase of hydrogen pressure ensures complete hydrogenation of the intermediates and final products, minimizing undesired side reactions and cracking, improving the yield of C₂₃-NA (Figure 5B). Under all reaction temperatures explored (150 – 220°C), the reactant was completely converted. With increasing reaction temperature, the yield of neo acid increased up to 180°C and then decreased (Figure 5C). These results suggest that at higher temperatures, the neo acid might undergo side reactions leading to high molecular weight species not detected by GC/GCMS. Lastly, a time-dependent study

was conducted. At time zero, which is the pre-heating time, all the reactant has converted but no C_{23} -NA was detected. As the reaction proceeds, C_{23} -NA starts forming but plateaus after 30 min (Figure 5D). Parameter optimization leads to 40% yield of C_{23} -NA and 15% yield of C_{14} -IA at Pd/C:Al(OTf)₃ ratio of 2:6, 3 MPa H₂, 180°C, 30 min, and cyclohexane as the solvent.



Figure 5 Effect of reaction parameters on product distribution for the HDO reaction. A) Catalyst molar ratio, B) H₂ pressure, C) Temperature, and D) Time. Reaction conditions: A) 1 mmol FNA, 10 mL cyclohexane, 3 MPa H₂, 180°C, 1 h, 500 rpm. B) 1 mmol FNA, 6 mol% Al(OTf)₃, 2 mol% Pd/C, 10 mL cyclohexane, 180°C, 1 h, 500 rpm. C) 1 mmol FNA, 6 mol% Al(OTf)₃, 2 mol% Pd/C, 10 mL cyclohexane, 3 MPa H₂, 1 h, 500 rpm. D) 1 mmol FNA, 6 mol% Al(OTf)₃, 2 mol% Pd/C, 10 mL cyclohexane, 3 MPa H₂, 1 h, 500 rpm. D) 1 mmol FNA, 6 mol% Al(OTf)₃, 2 mol% Pd/C, 10 mL cyclohexane, 180°C, 3 MPa H₂, 500 rpm.

To understand the plateau after 30 min, several hypotheses were tested. A certain amount of water was added to the reaction mixture at the optimized reaction conditions. The results confirmed no detrimental effect on neo acid production (Figure A.10A). FNA and HDO reaction intermediates could form high-molecular weight species, poisoning or blocking the active sites of the catalyst. Fresh catalyst added showed no improvements in product yields (Figure A.10B). To check if the side reactions from - COOH group cause the carbon loss, the -COOH group protection was performed by esterification of FNA with methanol, making furan-containing neo ester (FNE), which was then subjected to ring-opening (Table A.7). All FNE converted at 1 h and yield of C₂₄-NE increases slowly with time, but the yields and total carbon balance were lower compared to FNA HDO (Figure A.11). These investigations and literature evidence⁵⁰ suggest that reactant and intermediates participate into side reactions.

Chapter 4

CONCLUSIONS

Neo acids are commercially manufactured from petroleum derived olefins through the Koch synthesis under harsh reaction conditions using acids and multi-step purifications. Here, we demonstrated a strategy to synthesize renewable neo acids from biomass-derived 2-alkylfurans and keto acids through C-C coupling of the furans via hydroxyalkylation/alkylation (HAA) followed by ring-opening via hydrodeoxygenation (HDO) of furans. HAA reaction between 2-pentylfuran (2-PF) and levulinic acid (LA) produced furan based neo-acid precursors (FNA and FNA RO) in 90% yield over a solid acid catalyst. A 40% yield of the desired neo acids (C₂₃-NA) was obtained with 15% of C₁₄-NA product.

REFERENCES

1. M. A. Perea-Moreno, E. Samerón-Manzano and A. J. Perea-Moreno, *Sustainability*, 2019, **11**, 863.

2. N. Tripathi, C. D. Hills, R. S. Singh and C. J. Atkinson, C. J., *npj Clim. Atmos. Sci.*, 2019, **2**, 35.

3. S. Dutta and B. Saha, ACS Catal., 2017, 7, 5491–5499.

4. S. Liu, T. R. Josephson, A. Athaley, Q. P. Chen, A. Norton, M. Ierapetritou, J. I. Siepmann, B. Saha and D. G. Vlachos, *Sci. Adv.*, 2019, **5**, eaav548.

5. R. E. Patet, N. Nikbin, L. Williams, S. K. Green, C. Chang, W. Fan, S. Caratzoulas, P. J. Dauenhauer and D. G. Vlachos, *ACS Catal.*, 2015, **5**, 2367–2375.

6. O. A. Abdelrahman, D. S. Park, K. P. Vinter, C. S. Spanjers, L. Ren, H. J. Cho, D. G. Vlachos, W. Fan, M. Tsapatsis and P. J. Dauenhauer, *ACS Sustainable. Chem. Eng.*, 2017, **5**, 3732–3736.

7. D. S. Park, K. E. Joseph, M. Koehle, C. Krumm, L. Ren, J. N. Damen, M. H. Shete, H. S. Lee, X. Zuo, B. Lee, W. Fan, D. G. Vlachos, R. F. Lobo, M. Tsapatsis and P. J. Dauenhauer, *ACS Cent. Sci.*, 2016, **2**, 820–824.

8. M. Fefer, J. Am. Oil Chem. Soc., 1978, 55, A342–348.

9. V. M. Dembitsky, *Lipids*, 2006, **41**, 309–340.

10.ExxonMobil,Branchedalcohols,https://www.exxonmobilchemical.com/en/products/branched-alcohols,(accessed 28February 2023).

11. C. D. Collins in *Phytoremediation: Methods and Reviews, Vol. 23* (Ed.: N. Willey), Humana Press Inc., Totowa, 2007, pp. 99 – 108.

12. D. R. Bassett, J. Coat. Technol., 2001, 73, 43–55.

13.ExxonMobil,Branchedhigherolefins,https://www.exxonmobilchemical.com/en/products/branched-higher-olefins,(accessed28February 2023).

14. Paint & Coatings Industry Magazine. Novel 1K and 2K Moisture Curing Vinyl Alkoxysilane Technology, 2019, https://www.pcimag.com/articles/106704-novel-1k-and-2k-moisture-curing-vinyl-alkoxysilane-technology, (accessed 28 February 2023).

15. M. Research, Fatty Amines Market by Type, End Use, Function, Region - Global Forecast to 2024. https://www.marketresearch.com/MarketsandMarkets-v3719/Fatty-Amines-Type-Primary-Secondary-12979635/, (accessed 28 February 2023).

16. W. H. E. Mueller and M. Hartmann, *US Pat.*, US5342979A, Evonik Operations GmbH, 1994.

17. M. Fefer and A. J. Rutkowski, J. Am. Oil Chem. Soc., 1968, 45, 5–10.

18. R. W. Haushalter, W. Kim, T. A. Chavkin, L. The, M. E. Garber, M. Nhan, P. D. Adams, C. J. Petzold, L. Katz and J. D. Keasling, *Metab. Eng.*, 2014, **26**, 111–118.

19. T. Dulermo, F. Coze, M.-J. Virolle, V. Méchin, S. Baumberger and M. Froissard. *OCL - Oilseeds fats Crops Lipids*, 2016, **23**, A202.

20. E. J. Steen, Y. Kang, G. Bokinsky, Z. Hu, A. Schirmer, A. McClure, S. B. del Cardayre and J. D. Keasling, *Nature*, 2010, **463**, 559–562.

21. X.-L. Li, K. Zhang, J.-L. Jiang, R. Zhu, W.-P. Wu, J. Deng and Y. Fu, *Green Chem.*, 2018, **20**, 362–368.

22. J.-P. Lange, E. van der Heide, J. van Buijtenen and R. Price, ChemSusChem, 2012, 5, 150–166.

23. Y. Nakagawa, M. Tamura and K. Tomishige. ACS Catal., 2013, 3, 2655–2668.

24. F. D. Pileidis and M.-M Titirici, ChemSusChem, 2016, 9, 562–582.

25. S. Li, W. Deng, S. Wang, P. Wang, D. An, Y. Li, Q. Zhang and Y. Wang, *ChemSusChem*, 2018, **11**, 1995–2028.

26. A. M. Norton, S. Liu, B. Saha and D. G. Vlachos, *ChemSusChem*, 2019, **12**, 4780–4785.

27. A. Corma, O. de la Torre and M. Renz, *Energy Environ. Sci.*, 2012, 5, 6328–6344.

28. A. D. Sutton, F. D. Waldie, R. Wu, M. Schlaf, L. A. Silks 3rd and J. C. Gordon, *Nat. Chem.*, 2013, **5**, 428–432.

29. W. Wang, N. Li, S. Li, G. Li, F. Chen, X. Sheng, A. Wang, X. Wang, Y. Cong and T. Zhang, *Green Chem.*, 2016, **18**, 1218–1223.

30. S. Chen and C. Zhao, ACS Sustainable Chem. Eng. 2021, 9, 10818–10826.

31. S. Dutta, A. Bohre, W. Zheng, G. R. Jenness, M. Núñez, B. Saha and D. G. Vlachos, *ACS Catal.*, 2017, 7, 3905–3915.

32. A. Corma, O. de la Torre, M. Renz and N. Villandier, *Angew. Chem., Int. Ed.*, 2011, **50**, 2375–2378.

33. G. Li, N. Li, Z. Wang, C. Li, A. Wang, X. Wang, Y. Cong and T. Zhang, *ChemSusChem*, 2012, **5**, 1958–1966.

34. S. Liu, R. Bhattacharjee, S. Li, A. Danielson, T. Mazal, B. Saha and D. G. Vlachos, *Green Chem.*, 2020, **22**, 7896–7906.

35. S. Liu, B. Saha and D. G. Vlachos, *Green Chem.*, 2019, **21**, 3606–3614.

36. P. Ferrini, S. F. Koelewijn, J. Van Aelst, N. Nuttens and B. F. Sels, *ChemSusChem*, 2017, **10**, 2249–2257.

37. E. O. Ebikade, S. Sadula, S. Liu and D. G. Vlachos, *Green Chem.*, 2021, 23, 10090–10100.

38 T. Mochizuki, K. Kakinuma, M. Uchida, S. Deki, M. Watanabe and K. Miyatake, *ChemSusChem*, 2014, **7**, 729–733.

39 C. Wang and S. J. Paddison, *Soft Matter*, 2014, **10**, 819–830.

40 V. S. Likhomanov, O. N. Primachenko and S. S. Ivanchev. *Russ. J. Appl. Chem.*, 2014, **87**, 1314–1318.

41 S. So, H. Kang, D. Choi and K.-H Oh, *Int. J. Hydrogen Energy*, 2020, **45**, 19891–19899.

42 N. Nikbin, S. Caratzoulas and D. G. Vlachos, *ChemSusChem*, 2013, 6, 2066–2068.

43 M. J. Gilkey, R. Balakumar, D. G. Vlachos and B. Xu, *Catal. Sci. Technol.*, 2018, **8**, 2661–2671.

44 A. V. Tran, S.-K. Park, H. J. Lee, T. Y. Kim, Y. Kim, Y.-W. Suh, K.-Y. Lee and Y. J. Kim, *ChemSusChem*, 2022 **15**, e202200375.

45 H. L. Ngo, R. O. Dunn, B. Sharma and T. A. Foglia, *Eur. J. Lipid Sci. Technol.*, 2011, **113**, 180–188.

46 T. L. Lohr, Z. Li, R. S. Assary, L. A. Curtiss and T. J. Marks, *Energy Environ. Sci.*, 2016, **9**, 550–564.

47 J. Zhou, R. Zhu, J. Deng and Y. Fu, *Green Chem.*, 2018, **20**, 3974–3980.

48 Z. Li, R. S. Assary, A. C. Atesin, L. A. Curtiss and T. J. Marks, *J. Am. Chem. Soc.*, 2013, **136**, 104–107.

49 J. Keskiväli, P. Wrigstedt, K. Lagerblom and T. Repo, *Appl. Catal. A*, 2017, **534**, 40–45.

50 J. Keskiväli, A. Parviainen, k. Lagerblom and T. Repo, *RSC Adv.*, 2018, **8**, 15111–15118.

51 D. R. Parkinson, Analytical Techniques for Scientists, Elsevier, 2014.

52 Y. Wang, T.-Y. Chen and D. G. Vlachos, *J. Chem. Inf. Model.*, 2021, **61**, 5312–5319.

53 Q. Xia, Y. Xia, J. Xi, X. Liu, Y. Zhang, Y. Guo and Y. Wang, *ChemSusChem*, 2017, **10**, 747–753.

54 B. A. Ogunnaike, *Random phenomena : fundamentals of probability and statistics for engineers*, CRC Press, Boca Raton, 2010.

55 G. E. P. Box and N. R. Draper, *Empirical model-building and response surfaces*, Wiley, 1987.

56 E. R. Gunawan and D. Suhendra, *Indones. J. Chem.*, 2010, **8**, 83–90.

57 O. O. Awolu and S. K. Layokun, Int. J. Energy Environ. Eng., 2013, 4, 1–9.

58 L. Zhou, J. Yao, Z. Ren, Z. Yu, and H. Cai, *Energies*, 2020, **13**, 2754.

59 I. G. Moorthy, J. P. Maran, S. Ilakya, S. L. Anitha, S. P. Sabarima and B. Priya, *Ultrason. Sonochem.*, 2017, **34**, 525–530.

60. E. Andini, J. Bragger, S. Sadula and D. G. Vlachos, Green Chem., 2023, **25**, 3493–3502.

Appendix A





Figure A.1. The synthesis of furan, 2-methylfuran, 2-alkylfuran, levulinic acid, and pyruvic acid.

	Catalyst									
Compound	APW79S	SiO ₂ - Al ₂ O ₃ (Si/Al=5)	H-Y (Si/Al=30)	Al-MCM- 41 (Si/Al=25)	APW98	РТА	РМА	H_2SO_4	CH ₃ SO ₃ H	P-TSA
2-PF conversion (%)	99.0	18.9	23.0	19.6	81.8	99.9	97.0	76.2	89.7	91.2
LA conversion (%)	82.1	9.4	3.8	53.7	66.3	84.0	77.6	65.8	66.2	66.4
FFA yield (%)	87.3	0.1	1.4	0.3	59.8	76.1	65.5	62.8	59.9	60.8
PFSCs yield (%)	6.2	0.9	1.0	0.6	5.8	7.8	15.8	5.2	5.2	6.9
FFA RO yield (%)	2.8	0.1	0.0	0.1	1.0	6.0	2.1	2.0	6.4	7.5
Total C Balance (%)	100.9	84.2	83.5	73.9	88.2	93.4	90.7	96.1	86.9	89.4

Table A.1. Summary of catalyst screening. Reaction conditions: 20 mmol 2-pentylfuran (2-PF), 10 mmol levulinic acid (LA), 0.107 mmol H⁺ catalyst, 65°C, 6 h, 800 rpm.



Figure A.2. Reaction mechanism for the condensation of 2-pentylfuran with levulinic acid.

The mechanism of HAA has been well studied and the HAA reaction mechanism of 2-alkylfuran with ketone and levulinic acid with phenol has been reported.^{1,2} A plausible HAA reaction mechanism of 2-PF with LA (Figure A.2) over Aquivion PW79S was deduced considering the properties of the catalyst and the products. The hydroxyalkylation step is initiated by the protonation of the ketone group on LA by the catalyst, resulting in a carbocation intermediate (1). Then, the carbocation intermediate is attacked by a 2-PF molecule, forming the monomer (2). The alkylation step proceeds with the dehydration of the monomer, which entails proton transfer from furan ring to the carbonyl oxygen of the ketone and is the rate-determining step, resulting in another carbocation (3). Subsequently, the carbocation is alkylated by another 2-PF molecule, yielding the dimer or FFA (4). The carboxyl group on LA does not participate in the reaction as the presence of extra oxygen allows for delocalization of electrons, which provides extra stability.



Figure A.3. GC chromatogram overlay of the A) HAA chemistry between 2-PF and LA and blank experiments of B) 2-Pentylfuran and C) Levulinic Acid.

Table A.2. Initial HAA reaction rate data. $E_a = 34.3 \text{ kJ/mol}$ (M = molar). The formation rate refers to FNA.

Tomporaturo (°C)	r _{consumptic}	r (N4/c)	
Temperature (C)	2-PF	LA	formation (101/5)
35	0.051	0.057	0.036
45	0.130	0.038	0.062
55	0.196	0.043	0.081

Tab	le A.3.	Properties	of co	mmercial	solid	acid	catal	lysts.
-----	---------	------------	-------	----------	-------	------	-------	--------

Entry	Catalyst	Acid Density (H ⁺ mmol/g)	Surface Area (m ² /g)	Pore Diameter (nm)	Form	Reference
1	Aquivion PW79S	1.26	<1	-	Powder	3
2	Aquivion PW98	1	<1	-	Powder	4
3	Phosphotungstic Acid	1.04	<1	-	Powder	5,6
4	Phosphomolybdic Acid	1.5	1-5	-	Powder	7,8
5	HY	0.31	780	~0.7	Powder	9



Figure A.4. Effect of geometry. Reaction conditions: 20 mmol 2-pentylfuran (2-PF), 10 mmol levulinic acid (LA), 0.107 mmol H+ (0.085 g) Aquivion PW79S, 65°C, 800 rpm. (RBF = round bottom flask, SV = scintillation vial).

Reaction optimization using active learning

The yield of the products was optimized using active learning (see Methods). 16 points using a Latin hypercube sampling (LHS) were selected with varying temperature, reaction time, molar ratio, and catalyst loading. The LHS was selected due to its ability to sample efficiently a multidimensional parameter space. NEXTorch then processes the data and predicts optima where 4 subsequent sampling points are generated per iteration. The optimum overall FNA and FNA RO yield found in experiments vs. iteration number is plotted in Figure A.6A. The data is listed in Table A.4. The yield increased at the first iteration but decreased in the third and fourth iterations. This occurs as the algorithm suggests an optimum around the edge points where one of the input parameters takes its extreme value. In the following iterations, since the algorithm has sampled enough in the region (i.e., exploitation), it explores other parts to improve the model's overall accuracy. The decrease in the optimum yield of iterations three and four suggests an exploration with no increased product. The optimum neo-acid precursors on the first

iteration require more catalyst and longer reaction time compared to the initial LHS point (Table A.4). This process highlights the utility of a data-driven approach for optimizing product yield. If a traditional central composite DOE with four factors were used, at least 80 experiments would have been needed, which might still not cover the true optimum. NEXTorch efficiently reduced experimental time (<30 runs to identify an optimum) and consumables.

Exp	Trial	Т (С)	Catalyst Loading (mmol H+)	Time (h)	Molar Ratio (mol/mol)	2-PF Conv. (%)	LA Conv. (%)	FNA Yield (%)	FNA RO Yield (%)	FNA + FNA RO Yield (%)	PFSCs Yield (%)	Total C Balance (%)
0	0	76	0.196	4	2.77	99.1	98.2	77.8	5.6	83.3	10.4	94.8
1	0	69	0.13	11	1.80	99.6	77.7	84.7	5.2	90.0	5.21	100.7
2	0	63	0.174	1	1.96	57.9	49.9	49.9	0.3	50.2	3.41	97.5
3	0	96	0.253	11	2.36	99.8	93.9	65.8	8.1	74.0	8.9	84.2
4	0	86	0.094	10	2.23	99.6	88.9	79.2	6.1	85.3	6.3	94.1
5	0	57	0.123	7	1.55	98.1	63.4	83.0	1.5	84.5	4.5	99.9
6	0	98	0.148	10	2.43	99.7	92.4	68.5	7.3	75.9	7.9	85.4
7	0	75	0.071	5	1.48	99.8	62.4	80.4	4.5	85.0	4.59	100.0
8	0	83	0.103	8	1.10	99.9	54.7	61.0	8.8	69.8	3.2	88.2
9	0	52	0.226	3	1.63	79.9	59.1	67.7	0.5	68.1	4.2	97.6
10	0	93	0.052	2	2.88	96.9	89.1	69.8	3.7	73.5	11.1	89.0
11	0	56	0.179	9	1.38	99.4	61.1	81.8	2.4	84.2	4.3	100.0
12	0	70	0.258	6	2.57	99.4	98.0	80.8	5.9	86.7	8.7	96.2
13	0	60	0.294	4	1.16	99.8	54.7	78.2	3.7	81.9	4.9	101.6
14	0	88	0.21	7	2.70	99.7	96.3	72.7	8.0	80.7	9.7	91.3
15	0	65	0.107	6	2.00	99.0	82.1	87.3	2.8	90.1	6.2	100.9
16	1	65	0.122	8	2.09	99.5	82.7	83.9	3.4	87.4	5.4	96.8
17	1	66	0.051	7	1.99	98.0	72.2	79.4	1.5	80.9	5.6	94.0
18	1	66	0.170	7	1.98	99.8	81.8	86.2	4.9	91.1	6.0	101.3
19	1	58	0.120	7	2.34	91.8	81.4	78.4	1.3	79.8	5.3	95.2
20	2	67	0.182	6	1.82	99.9	72.8	79.19	4.4	83.6	6.2	96.2
21	2	63	0.209	10	2.06	99.9	84.2	81.36	5.9	87.3	6.7	97.4
22	2	59	0.263	7	1.76	99.9	72.3	81.19	4.3	85.5	5.9	98.1
23	2	62	0.083	11	2.23	99.2	85.2	84.25	2.7	87.0	6.1	96.7
24	3	55	0.114	11	1.75	97.0	63.6	75.3	1.3	76.6	4.9	92.5

Table A.4. Summary of multi-parameter optimization using NEXTorch. First 15 runs are the initial dataset. 4 additional runs added at each iteration. Parameters varied = temperature, time, catalyst loading, and molar ratio.

25	3	73	0.069	12	2.17	99.4	80.2	77.5	3.3	80.7	5.7	90.9
26	3	73	0.115	6	2.23	99.6	83.6	78.4	3.9	82.3	6.4	92.3
27	3	70	0.126	10	2.28	99.7	84.5	76.7	5.2	81.9	6.9	92.1

Understanding the correlation between parameters via machine learning

Principal component analysis (PCA) was performed to understand the effect of reaction conditions on product distribution. PCA reduces dimensionality, identifies independent factors, and reveals correlations and significance of factors.^{10,11} Our dataset consists of 10 features; four are reaction conditions (temperature, time, molar ratio, and catalyst loading) and the rest entail conversions and yields (2-PF conversion, LA conversion, FNA yield, FNA RO yield, PFSCs yield, and total carbon balance). The scree plot (Figure A.5) shows that three principal components explain 75% of the variation and are sufficient for exploratory analysis. Generally, factors clustered together show a strong positive correlation, and those orthogonal to each other show little or no correlation. Factors on opposite sides are inversely correlated.



Figure A.5. Scree plot of PCA analysis.

The two principal components that account for most of the variability are shown in the loading plot (Figure A.6B). The results clearly show two clusters: group 1 includes 2-PF conversion and time, and group 2 consists of the LA conversion, FNA RO yields, PFSCs yield, molar ratio, and temperature. 2-PF conversion is positively correlated with the reaction time. Additionally, there is a clear correlation between FNA yield and 2-PF conversion with reaction time; the longer the reaction time, the more 2-PF converts and the more FNA forms. The reaction time (group 1) is nearly antiparallel with catalyst loading and total carbon balance, indicating an inverse relation between them, *i.e.*, as the catalyst loading increases, less reaction time is required and as the reaction time increases, the reactants and products participate in side-reactions forming byproducts, resulting in the lower carbon balance. This fact indicates a tradeoff between increasing catalyst loading and conversion of 2-PF.



Figure A.6. Multi-parameter optimization using NEXTorch for the HAA reaction. A) Optimal overall FNA and FNA RO yield (%) from experiments in each iteration. The error bar indicates the standard deviation from 2 measurements. B) Principal

component analysis of the correlations between reaction conditions and products. C) Correlation matrix of reaction conditions and outcomes. The green and red colors indicate strong positive and negative correlations between two features, respectively.

The reaction time is almost orthogonal with LA conversion and FNA RO and PFSCs yields, *i.e.*, it does not affect them. These phenomena occur due to (a) LA is an electrophile and its conversion is dependent on the reactivity of the nucleophile, (b) the formation of FNA RO is due to participation of the water by-product, and (c) the formation of PFSCs is due to 2-PF's tendency to self-condense due to its reactivity. Catalysts that could suppresses the self-condensation of 2-PF will be important for future work. LA conversion and FNA RO and PFSCs yields are positively correlated with temperature and reactant's molar ratio. Regarding LA, the high conversion could be due to forming angelica lactones¹² rather than FNA. Maximov et el. reported the formation of angelica lactones from levulinic acid in over an acidic catalyst at 80 -120°C. FNA yield is inversely correlated with temperature, and temperature is inversely correlated (strongly) to total C balance, as well as the rest of cluster 2 (weakly). As temperature increases, FNA participates in undesirable side reactions resulting in the lower carbon balance. This fact suggests that a moderate temperature is preferable for HAA chemistries. With the data from multi-parameter optimization, we generated a correlation matrix to further clarify interactions between variables (Figure A.6C). The resulting matrix agrees with the observations deduced from the PCA results shown in Figure A.6B.

Table A.5. Detailed experimental results of HAA reaction between different 2alkylfurans and keto acid of varying molecular sizes. Reaction Conditions: 20 mmol 2alkylfuran, (2-alkylfuran/keto acid) (mol/mol) = 2, 0.107 mmol H⁺ Aquivion PW79S, 6 h, 65°C, 800 rpm.

Entry	Reage	nts	#C	R Conv.	Keto Acid	Yield	Total C	% Error of	
	R	Keto Acid		(%)	Conv. (%)	FNA & FNA RO (%)	Balance (%)	FNA & FNA RO Yield	
1	Methyl	LA	C15	96.5	58.4	47.3	75.1	0.9	
2	Ethyl	LA	C17	99.8	69.4	76.7	94.4	1.2	
3	n-Propyl	LA	C19	95.7	78.6	86.9	101.9	0.6	
4	n-Butyl	LA	C21	99.9	78.1	74.9	87.1	2.0	
5	n-Pentyl	LA	C23	99.5	83.6	90.1	100.9	0.1	
7	n-Heptyl	LA	C27	99.3	83.0	82.0	89.4	0.2	
8	Methyl	PA	C13	97.4	95.8	85.6	93.2	0.4	
9	Ethyl	PA	C15	99.2	99.7	87.2	89.6	2.9	
10	n-Propyl	PA	C17	97.9	99.6	91.9	95.1	0.4	
11	n-Butyl	PA	C19	99.9	99.6	89.6	92.2	0.9	
12	n-Pentyl	PA	C21	98.4	99.8	85.5	89.0	2.5	
14	n-Heptyl	PA	C25	96.9	99.2	79.2	84.0	0.2	



Figure A.7. FT-IR spectra of fresh and used Aquivion PW79S catalysts.

Table A.6. The effect of catalysts on product distribution. Reaction conditions: 1 mmol FNA, 6 mol% Al(OTf)₃, 2 mol% Pd/C, 10 mL cyclohexane, 3 MPa H₂, 180°C, 30 min and 750 rpm.

Catalvet(e)	FNA + FNA RO	C23-NA	C14-IA yield	Hydrogenated FNA		
Cataryst(s)	Conversion (%)	yield (%)	(%)	yield (%)		
$Al(OTf)_3 + Pd/C$	100	40	15	0		
Al(OTf) ₃ only	91	0	0	0		
Pd/C only	100	0	0	100		
Blank (no catalysts)	0	0	0	0		



Figure A.8. GC overlay for the HDO product mixture obtained with and without a catalyst. A) HDO reaction over $Al(OTf)_3 + Pd/C$ catalysts, B) HDO reaction over $Al(OTf)_3$ only (without hydrogenation catalyst), C) HDO reaction over Pd/C only (without metal triflate), D) HDO reaction without any hydrogenation catalyst and metal triflate (Blank reaction). Reaction conditions: 1 mmol FNA, 6 mol% $Al(OTf)_3$, 2 mol% Pd/C, 10 mL cyclohexane, 3 MPa H₂, 180°C, 1 h, 500 rpm.



Figure A.9. LCMS of HDO product solution. Reaction conditions: 1 mmol FNA, 6 mol% Al(OTf)₃, 2 mol% Pd/C, 10 mL cyclohexane, 3 MPa H₂, 180°C, 1 h, 500 rpm.



Figure A.10. Effect of A) water addition. Reaction conditions: 1 mmol FNA, 6 mol% Al(OTf)₃, 2 mol% Pd1/C, 10 mL cyclohexane, 3 MPa H₂, 180°C, 1 h, and 750 rpm. 1 drop of water = \sim 40 mg, and B) used catalyst removal. Reaction conditions: 1 mmol FNA, 6 mol% Al(OTf)₃, 2 mol% Pd/C, 10 mL cyclohexane, 3 MPa H₂, 180°C, 30 min, and 750 rpm. The reaction mixture was then added into a new reactor with fresh catalysts and reacted for 30 min.

Table A.7. Esterification of FNA with alcohol (methanol) making FNE.FNA conversion and FNE purity upon esterification of FNA with alcohol. Reaction conditions: 4 g FNA, 16 mL methanol, 2 MPa N₂, 200°C, 4 h.





Figure A.11. Time-dependent study of FNE ring-opening. Reaction conditions: 1 mmol FNE, 6 mol% Al(OTf)₃, 2 mol% Pd/C, 10 mL cyclohexane, 3 MPa H₂, 180°C, and 750 rpm.

References

- 1. S. Liu, R. Bhattacharjee, S. Li, A. Danielson, T. Mazal, B. Saha and D. G. Vlachos, *Green Chem.*, 2020, 22, 7896–7906.
- 2. S. Van de Vyver, S. Helsen, J. Geboers, F. Yu, J. Thomas, M. Smet, W. Dehaen, Y. Román-Leshkov, I. Hermans and B. F. Sels, *ACS Catal.*, 2012, 2, 2700–2704.
- 3. S. Liu, B. Saha and D. G. Vlachos, Green Chem., 2019, 21, 3606–3614.
- 4. A. Karam, K. De Oliveira Vigier, S. Marinkovic, B. Estrine, C. Oldani and F. Jérôme, *ACS Catal.*, 2017, 7, 2990–2997.
- 5. A. Kuvayskaya, *Electronic Theses and Dissertations*, 2020, Paper 3738.
- 6. S. He, Y. Ai, W. Dai, S. Zhai, H. Song and J. Lin, *Polym. Test.*, 2021, 100, 107246.
- 7. R. S. Salama, S. M. Hassan, A. I. Ahmed, W. S. A. El-Yazeed and M. A. Mannaa, *RSC Adv.*, 2020, 10, 21115–21128.
- 8. H. C. Zhou, J. L. Song, Q. L. Meng, Z. H. He, Z. W. Jiang, B. W. Zhou, H. Z. Liu and B. X. Han, *Green Chem.*, 2016, 18, 220–225.
- 9. R. Weingarten, G. A. Tompsett, W. C. Conner and G. W. Huber, *J. Catal.*, 2011, 279, 174–182.
- 10. J. Lever, M. Krzywinski and N. Altman, *Nat. Methods*, 2017, 14, 641–642.
- 11. A. J. Medford, A. J., M. R. Kunz, S. M. Ewing, T. Borders and R. Fushimi, *ACS Catal.*, 2018, 8, 7403–7429.
- 12. A. L. Maximov, A. V. Zolotukhina, A. A. Mamedli, L. A. Kulikov and E. A. Karakhanov, *ChemCatChem*, 2017, 10, 222–233.

Appendix B

PERMISSIONS FOR REPRINT

All chapters were reproduced from Ref. 60 with permission from the Royal Society of Chemistry (<u>https://doi.org/10.1039/D3GC00735A</u>).