

Final Technical Report 2018: DOE DE-SC0005430
"Enabling Catalytic Strategies for Biomass Conversion"
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1. Scientific and/or Technical Merit of the Project

The goal of this DOE-funded project was to investigate the fundamental science related to the development of selective catalytic processes for converting renewable bio-feedstocks into new classes of value-added chemicals, renewable materials and thermoplastics. This research program combined fundamental investigations of coordination chemistry, kinetics and mechanism, *in-situ* investigation of catalytic intermediates, and the development of new patterns of catalytic reactivity for the selective synthesis of chemical intermediates, monomers and renewable polymers derived from biomass feedstocks.

Specific objectives were to: (1) Investigate the basic science of selective catalytic oxidation reactions, particularly of aerobic oxidations of biomass-derived polyols and carbohydrates; (2) Expand the scope of selective catalytic oxidations for the synthesis of new renewable monomers and polymers and (3) Develop integrated catalytic strategies for conversion of biomass wastes to useful chemical intermediates and polymers.

Accomplishments in the last grant period met and exceeded our initial objectives, as our investigations of Pd-catalyzed selective aerobic oxidation catalysis illuminated the diverse role of a novel trinuclear dicationic LPd_3O_2 intermediate that had been identified by *in-situ* mass spectrometry.¹⁻² During the course of the last grant period, we extended our previous investigations on the selective oxidation of polyols³⁻⁴ to develop new catalytic strategies for the selective oxidation of unprotected carbohydrates,⁵ and the selective oxidative lactonization of functionalized 1,5-diols to generate polymerizable lactone monomers and new functionalized polyesters.⁶ In collaborative studies, we illuminated the details of a novel oxidative spirolactonization reaction with the cationic Pd neocuproine catalyst,⁷ and developed integrated biochemical and chemical strategies for the utilization of waste biomass for monomer and polymer synthesis.⁸⁻¹¹

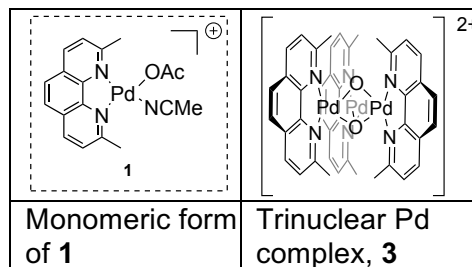
2. What was accomplished under these goals?

Description of Selected Key Results of Work Accomplished during the Previous Grant.

(a) *Role of multinuclear LPd_3O_2 species in aerobic oxidations and hydrogen-peroxide disproportionation reactions.* During the course of mechanistic investigations on the oxidation of alcohols with $[\text{LPd}(\text{OAc})_2(\text{OTf})_2]$ (**1**, L = neocuproine), we identified a novel bridging trinuclear palladium species, $[(\text{LPd}(\text{II}))_3(\text{}^3\text{-O})_2]^{2+}$, **3**, that forms in the course of the aerobic oxidation of 1,2-propane diol by $[\text{LPd}(\text{OAc})_2(\text{OTf})_2]$.¹ The identification of this novel complex was enabled by high-

resolution *in-situ* mass spectrometry, carried out in collaboration with the Zare group.¹⁻² Independent synthesis, structural characterization, and catalytic studies of **3** show that it is a product of oxygen activation by reduced palladium species and a competent intermediate in the catalytic aerobic oxidation of alcohols. The formation and catalytic activity of the trinuclear Pd_3O_2 species has illuminated a novel, multinuclear pathway for oxygen reduction by palladium.

The role of this compound in catalysis and its mechanism of formation have been investigated by a series of kinetics, isotope labeling, and reactivity studies.² The results suggest that the trinuclear

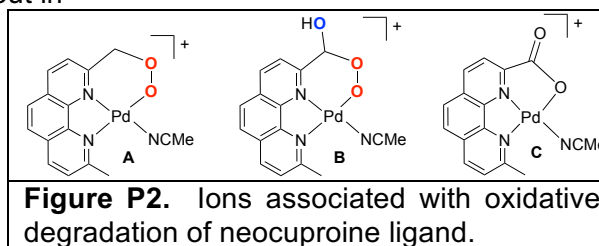
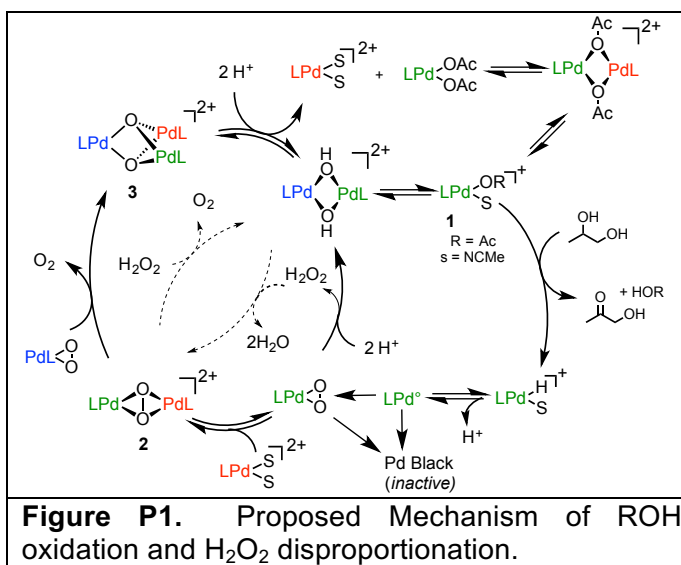


compound $[(\text{LPd}(\text{II}))_3(\text{}^3\text{-O})_2]^{2+}$ **3** is produced as an off-path species during both alcohol oxidation and disproportionation of hydrogen peroxide,² the initial product of oxygen reduction during catalysis. Subsequent investigations revealed that the cationic Pd complex (**1**) is a remarkably active hydrogen peroxide disproportionation catalyst and that H_2O_2 disproportionation occurs simultaneously with that of alcohol oxidation (Figure 1). Kinetics studies of hydrogen peroxide disproportionation reveal a complex dependence of the disproportionation rate on the concentration of Pd catalyst. Mass spectrometry and NMR monitoring of catalysis shows that **3** is produced during H_2O_2 disproportionation, where isotope labeling studies show that it is a product of H_2O_2 activation. Synthetic studies have shown that **3** can be converted to $[\text{LPd}(\text{OAc})_2](\text{OTf})_2$, however this process is too slow to be directly on-path for alcohol oxidation. This work provides strong evidence that **3** is an intermediate of a competitive parallel process during catalysis and hints at the importance of transient multinuclear palladium-oxygen intermediates in oxygen activation and hydrogen peroxide disproportionation in this system.² A suspected intermediate in the formation of **3**, a binuclear $\text{Pd}_2\text{-O}_2$ intermediate **2**, has also been detected by ESI-MS during alcohol oxidation and H_2O_2 disproportionation.

(b) *Improved Catalyst Lifetimes and Turnover Numbers:* Kinetic and mechanistic studies of alcohol oxidation with Pd catalyst **1** revealed a competitive oxidative degradation of the neocuproine ligand when O_2 or air is used as the terminal oxidant.¹² Several strategies were employed to illuminate the pathways for the competitive oxidative degradation of the $[\text{LPd}(\text{OAc})_2](\text{OTf})_2$ complex (neocuproine = 2,9-dimethyl-1,10-phenanthroline) during aerobic oxidations with the goal of increasing turnover numbers and enabling lower catalyst loadings. *In-operando* mass spectrometry studies, carried out in

collaboration with the Zare group at Stanford, revealed several ions whose intensities increased in an inverse correlation with the decrease in rate during the course of the aerobic oxidation reactions.² In particular, ions corresponding to the peroxo species **A** and **B** (Fig. 2) were identified during aerobic catalysis, whose structures were inferred by both MS/MS

fragmentation data and $^{18}\text{O}_2/\text{H}_2^{18}\text{O}$ isotopic labeling experiments. Complex **C**, which plausibly derive from species such as **A** and **B**, was previously isolated from aerobic reaction mixtures, characterized, and shown to be catalytically inactive. The peroxo complexes **A** and **B** are highly suggestive of a free-radical oxidative ligand degradation pathway initiated by hydrogen-atom abstraction from the neocuproine ligand. Guided by this hypothesis, we prepared the d_6 -ligand **E** and nitro-substituted ligand **F**, both of which resulted in modest increases in catalyst turnover numbers (from 35 to 54-59 mole ketone/mole Pd, Figure 3).¹³ These preliminary results are consistent with a hydrogen-atom abstraction step as a key initiating event in catalyst degradation. A variety of sacrificial reductants were also investigated. Aromatic solvents containing benzylic hydrogens exhibited modest improvements in catalyst turnover numbers; mechanistic studies revealed that benzylic hydroperoxides **H**, generated from oxidation of



ethylbenzene, were particularly effective as sacrificial hydrogen atom donors. Phenol anti-oxidants such as **G** proved a particularly useful additive for mitigating oxidative degradation of the catalyst.^{5,13}

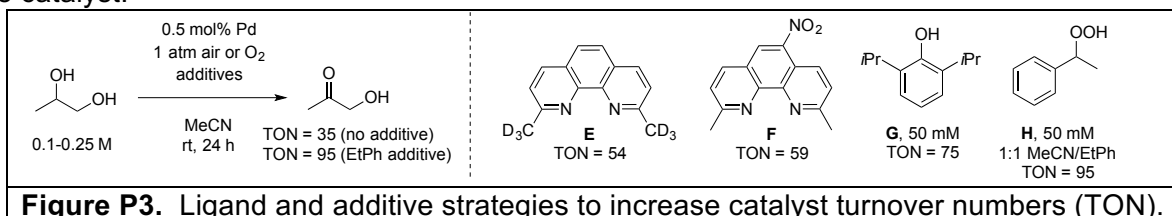
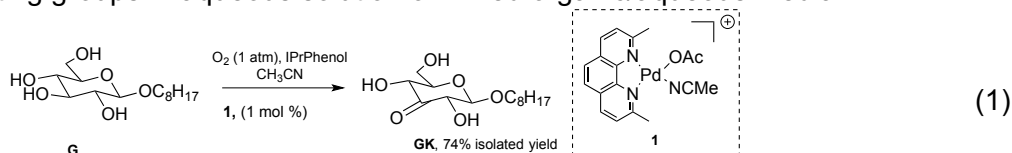


Figure P3. Ligand and additive strategies to increase catalyst turnover numbers (TON).

These insights enabled us to modify our aerobic oxidation protocols for the aerobic oxidation of a variety of polyols on a multigram scale with catalyst loadings as low as 0.25 mol % Pd; further extensions of these studies are described in the Project Narrative.

(c) *Chemoselective Catalytic Oxidations of Carbohydrates:* The scope of selective oxidations with these Pd catalysts were extended to carbohydrates, specifically the 6-carbon glucopyranosides and deoxy fucopyranosides as well as the 5-carbon ribopyranosides. DeVries and Minaard,¹⁴ stimulated by our earlier report on the selective oxidation of glycerol,³ recently reported that our Pd catalyst was able to selectively oxidize glycosides bearing exclusively equatorial hydroxyl groups, using benzoquinone or 2,6-dichlorobenzoquinone as the terminal oxidant. Significantly, the selective oxidations of sugars can be carried out in the absence of protecting groups in aqueous solution or mixed organic/aqueous media.



Armed with new insights on the role of phenol anti-oxidants for improving aerobic oxidations, we showed that the chemoselective oxidation of the unprotected alkyl glucosides **G** can be carried out aerobically with catalyst loadings as low as 1 mol% Pd to afford excellent yields of the 3-ketose **GK** in

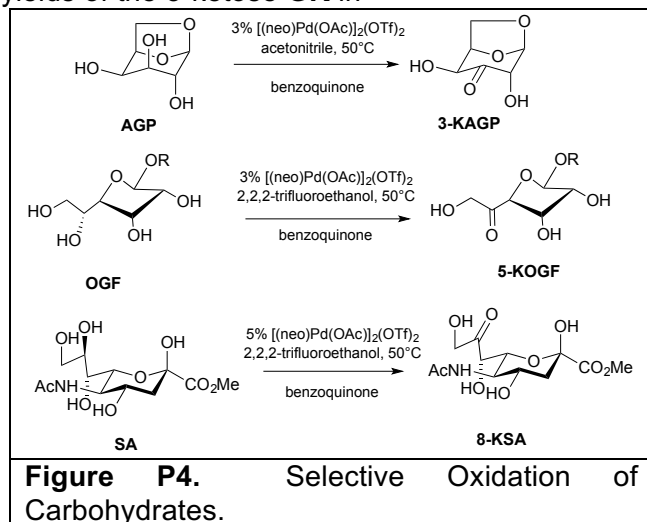


Figure P4. Selective Oxidation of Carbohydrates.

high chemoselectivity (eq. 1).⁵ The origin of the high selectivities of these oxidations remains an area of active investigation (see Project Narrative), but during the last grant, we carried out a series of investigations on the scope, selectivity and role of glycoside substituents and solvents on the chemoselectivity for the oxidation of unprotected carbohydrates.⁵ Notable examples include the selective oxidation of 1,6-anhydro-β-D-galactopyranoside **AGP** to the 3-ketose, of octyl-β-D-galactofuranoside **OGF** to the exocyclic 5-ketose, and of N-acetylneuraminic (sialic) acid methyl ester **SA** to the exocyclic 8-ketose (Figure 4).⁵

These results reveal that catalytic oxidations of unprotected carbohydrates, long restricted to the enzymes, can now be carried out efficiently with appropriate homogeneous catalysts.

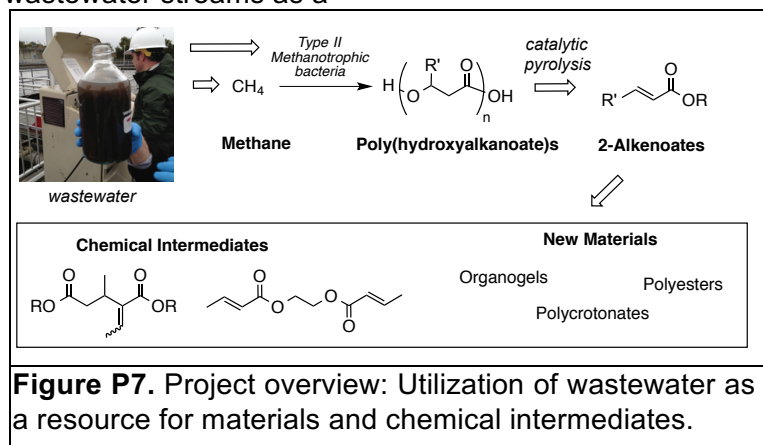
(d) *Scope and Utility of Chemoselective Catalytic Oxidations:* The scope of the Pd-catalyzed alcohol oxidations were also extended to the oxidative lactonization of substituted diethanolamines to

generate new families of morpholinones (aza lactones), which have proven a versatile class of monomers for generating functionalized, degradable

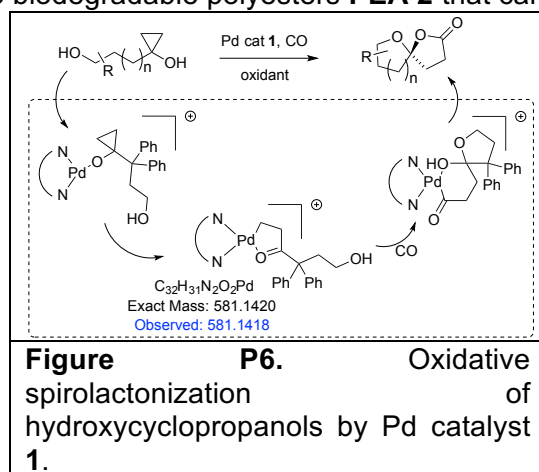
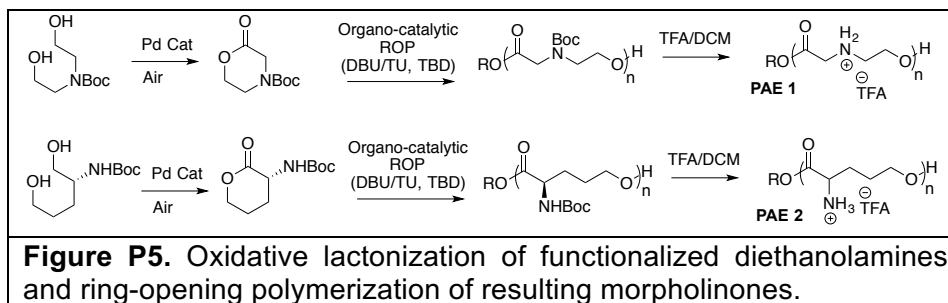
polyesters.⁶ Lactones accessed via the Pd-catalyzed oxidative lactonization of α - ω diols were polymerized (by organocatalytic ROP)¹⁵ to generate functionalized poly(-aminoester)s (PAEs) of precise molecular weight and low polydispersity.⁶ Removal of the Boc protecting group affords novel cationic, water soluble poly(aminoesters) PAEs (Figure 5) that are stable on the order of days (>0.5 M in D₂O, >72 hrs). The oxidative lactonization of the amino-diol derived from glutamic acid (Figure 5) provides a novel route to biodegradable polyesters **PEA 2** that can be generated from renewable resources. Thus, the high selectivities of these alcohol oxidation catalysts and their functional group tolerance has proven an enabling advance to generate new classes of monomers, and thus new families of functional materials.

Our collaborative studies with the Zare group on the use of *in-situ* mass spectrometry stimulated a new collaboration with Prof. Mingji Dai of Purdue. Prof. Dai and his students discovered a novel catalytic oxidative spirolactonization of hydroxycyclopropanols with our Pd catalyst **1**. This method generates spirolactones (Figure 6). Katherine Walker, a joint student in our group and Dick Zare's group, was able to identify several key intermediates in this novel reaction (Figure 6). this was described in a recent manuscript.⁷ Related studies with the Muldoon group utilized a similar methodology to interrogate the Wacker Oxidation of styrenes with Hydrogen Peroxide.¹⁶

(d) *Utilization of Wastewater as a Resource for Renewable Resources*: We have collaborated with Prof. Craig Criddle of Stanford to develop new strategies for utilizing wastewater streams as a



methanotrophs by addition of fatty acids to the bacteria as a co-substrate alongside methane.^{8,10-11,17} This breakthrough in copolymer production could have important industrial



source of chemical intermediates, monomers and polymers (Figure 7). Our approach combines biological and chemical catalysis, using the Criddle group's expertise in the isolation of methanotrophic bacteria from wastewater, as well as our group's expertise in chemical catalysis and polymer chemistry. We demonstrated that poly(3-hydroxybutyrate-co-3-hydroxy-valerate, PHBV) copolymers can be produced in

implications, as previous methanotrophic production of PHAs had been limited to the brittle and difficult-to-process poly(3-hydroxybutyrate) (PHB) homopolymers. ¹³C-labeling studies have confirmed the incorporation of the fatty acids. We have developed a novel recycling process for PHA's that consists of (1) a catalytic pyrolysis of medium-chain length (mcl) (C₆ – C₉) PHAs into their constituent 2-alkenoates, followed by (2) methanotrophic polymerization of the 2-alkenoates into short-chain length (scl) (C₄ - C₅) PHAs.¹¹ Significantly, the methanotrophs converted the even-numbered alkenoates to the PHB homopolymer while the mixture containing odd-numbered alkenoates was converted to PHBV copolymer.

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3. What opportunities for training and professional development has the project provided?

This project provided rich opportunities for graduate student training in the handling of air-sensitive compounds, catalytic oxidation reactions, kinetics and modeling, the development and application of in-situ techniques utilizing high resolution mass spectrometry. Collaborative investigations with Prof. Richard Zare (Stanford Chemistry) and Prof. Craig Criddle (Stanford Environmental Science and Engineering) have expanded the training opportunities of the graduate students involved to embrace novel physical methods (mass spectrometry) and molecular biology to address interesting questions and opportunities in biomass conversion strategies.

4. How have the results been disseminated to communities of interest?

Results of the research were disseminated through published manuscripts, public lectures at National, International and Regional meetings. Three manuscripts were published, and two were submitted for publication during the grant period; one manuscript is in the final stages of preparation. The P.I. Waymouth was invited to lecture at several conferences where he discussed recent advances supported by this project at the 12th International Symposium on Activation of Dioxygen and Homogeneous Oxidation Catalysis (ADHOC, June 21-25, Madison, Wisconsin), the International Symposium on Ionic Polymerization (July 5-10, 2015, Bordeaux, France), the Pacifichem Symposium (#301) "Homogeneous Catalysis for the Upgrading of Biomass Derived Molecules" in Hawaii (Dec. 18-20, 2015), the 250th National Meeting of the American Chemical Society (March 13, 2016), the Butler Lectureship (10 lectures, Aug 31 - Sept. 11, 2015; Feb 2 - Feb 26, 2016) and at the Butler Polymer Laboratory at the University of Florida.

Products.

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Impacts.

1. What is the impact on the development of the principal discipline(s) of the project?

The impacts of our discoveries of selective catalytic oxidation of polyols and especially of unprotected carbohydrates are significant as they demonstrate the power of selective homogeneous catalysis to effect efficient and selective reactions of polyfunctionalized substrates. Our work on the combination of mechanistic organometallic chemistry coupled with in-situ mass spectrometry are significant in illustrating the power of this analytic technique in illuminating reaction mechanisms.

2. What is the impact on other disciplines?

The ability to selectively functionalize unprotected carbohydrates by catalytic oxidation will have significant impacts on glycosciences, as the synthesis of natural and unnatural carbohydrates has traditionally been very challenging.

3. What is the impact on the development of human resources?

This research effort has provided opportunities for research, teaching and mentoring in a highly interdisciplinary research area that combines organic and organometallic synthesis, catalysis and the application and development of novel in-situ mass spectrometry to interrogate catalytic reaction mechanisms. During the course of the grant period, Andrew Ingram received his Ph.D.

and is now employed at Archer Daniels Midland. One of the graduate students that participated on this project is female, providing opportunities for talented women scientists to advance their education and professional development.

4. What is the impact on physical, institutional, and information resources that form infrastructure?

During the course of the grant period, Katherine Walker commissioned an inert-atmosphere drybox that could be interfaced to the Orbitrap Mass Spectrometer. This will expand our capability to interrogate catalytic reactions that require inert atmosphere conditions.

5. What is the impact on technology transfer?

A patent on the functionalization of lignin was awarded US Patent 9,567,432 B2 "Lignin Poly(lactic Acid) Copolymers, issued Feb. 14, 2017.