

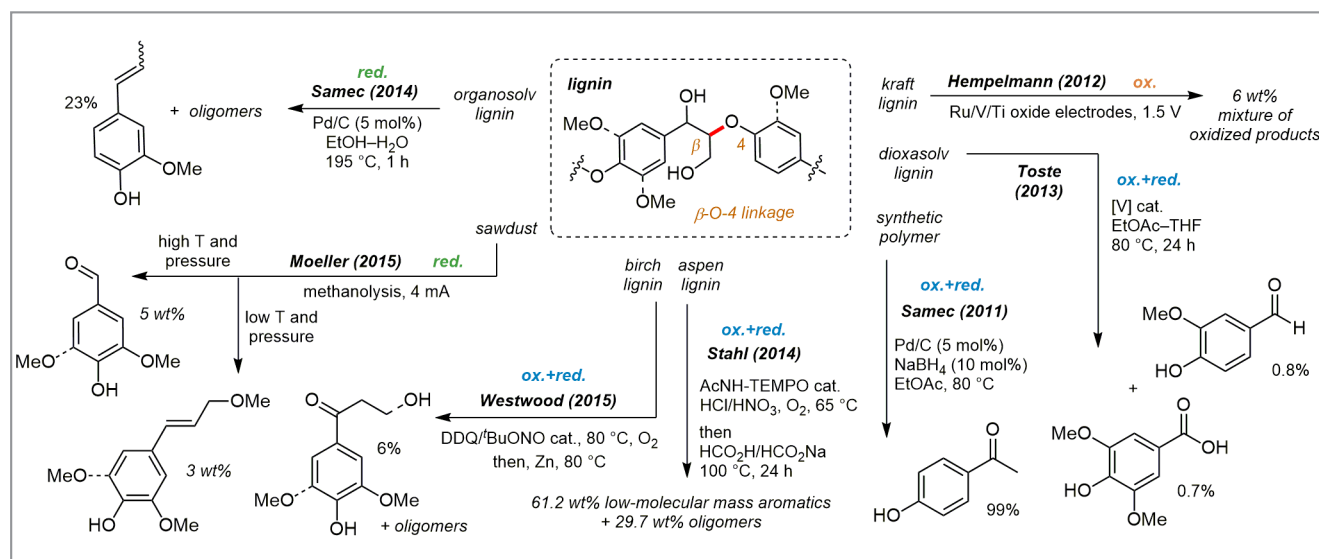
Redox Catalysis Facilitates Lignin Depolymerization

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The laboratory of Professor Corey Stephenson at the University of Michigan (Ann Arbor, USA) has had an interest in lignin depolymerization since 2014. “There were two main reasons that initially attracted our attention towards lignin: 1) its abundance and unique aromatic backbone, which makes it an exceptional renewable source for small aromatic chemicals, and 2) the few examples of selective methodologies found in the literature regarding its depolymerization, a majority of them employing harsh conditions due to its recalcitrant nature (Scheme 1),” explained Professor Stephenson. He continued: “Since the major interest of my laboratory focuses on harnessing the energy of visible light, we saw the opportunity of using photoredox catalysis to selectively cleave the β -O-4 bonds present in the lignin backbone, a methodology that proved to be exceptionally robust for lignin model systems (*J. Am. Chem. Soc.* 2014, 136, 1218). However, a prior oxidation step was required to achieve this fragmentation, which prompted us to search for alternative oxidation methodologies, such as the one presented in the present ACS Central Science publication.”

Electrocatalytic oxidation captured the group's attention as a suitable alternative to chemical oxidation due to

the simplicity of the reaction conditions, and the potential compatibility of the reaction conditions with the subsequent photocatalytic fragmentation. “Our initial attempts of driving this oxidation in bulk in the presence of known *N*-oxyl persistent radicals, such as TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) afforded low yields and irreproducible results in the oxidation of lignin model systems,” remarked Professor Stephenson. With the ultimate goal in mind of developing a methodology that could potentially be applicable on large scale, the authors searched for a robust, selective and inexpensive catalyst. “In this regard, we found that the oxidation potential of NHPI (*N*-hydroxyphthalimide) in the presence of a base, such as 2,6-lutidine, was relatively low (0.38 V vs Fc^+/Fc),” said Professor Stephenson, continuing: “By simple cyclic voltammetry (CV) analysis, we realized that this catalyst would selectively oxidize the secondary benzylic alcohol, leaving the pendant primary alcohol intact. This selectivity would give predictable fragments and cleaner fragmentation product mixtures.” The optimization of the process required several months since inconsistent results were obtained when different solvent mixtures, bases and substrate concentrations were evaluated. It was not until the possible mechanism for



Scheme 1 State-of-the-art of the current methodologies for the depolymerization of native lignin via oxidative (ox.), reductive (red.) or redox neutral approaches (ox. + red.). Adapted with permission from *ACS Cent. Sci.* 2017, 3, 621–628, DOI: 10.1021/acscentsci.7b00140, Copyright 2017 American Chemical Society.

this electrochemical oxidation was analyzed carefully that the group realized that the presence of molecular oxygen was beneficial for the catalysis. Indeed, an increased catalytic activity was observed in oxygen-sparged MeCN and also provided consistent results. Another key optimization factor was the change of the electrolyte. “It is usually assumed that the role of the electrolyte in an electrochemical cell is exclusively to provide conductivity to the reaction mixture, acting as a spectator in the overall electrochemical reaction,” explained Professor Stephenson. “However, in MeCN we observed the formation of a red precipitate in the mixture of NHPI, 2,6-lutidine and NaClO₄, a common electrolyte, only when the three components were present. This result clearly indicated the non-innocent role of the NaClO₄ electrolyte in our reaction. Although we have not been able to identify the precise nature of this precipitate, ¹H NMR analysis signals corresponding to both NHPI and 2,6-lutidine were observed when the precipitate was analyzed, indicating that part of the catalyst was being removed from the reaction mixture. Finally, KPF₆ proved to be a competent electrolyte since no precipitate was observed. Acid wash of the reticulated vitreous carbon (RVC) electrodes used in the reaction helped to provide more consistent results, which we believe is due to the introduction of oxygenated groups on the carbon surface.”

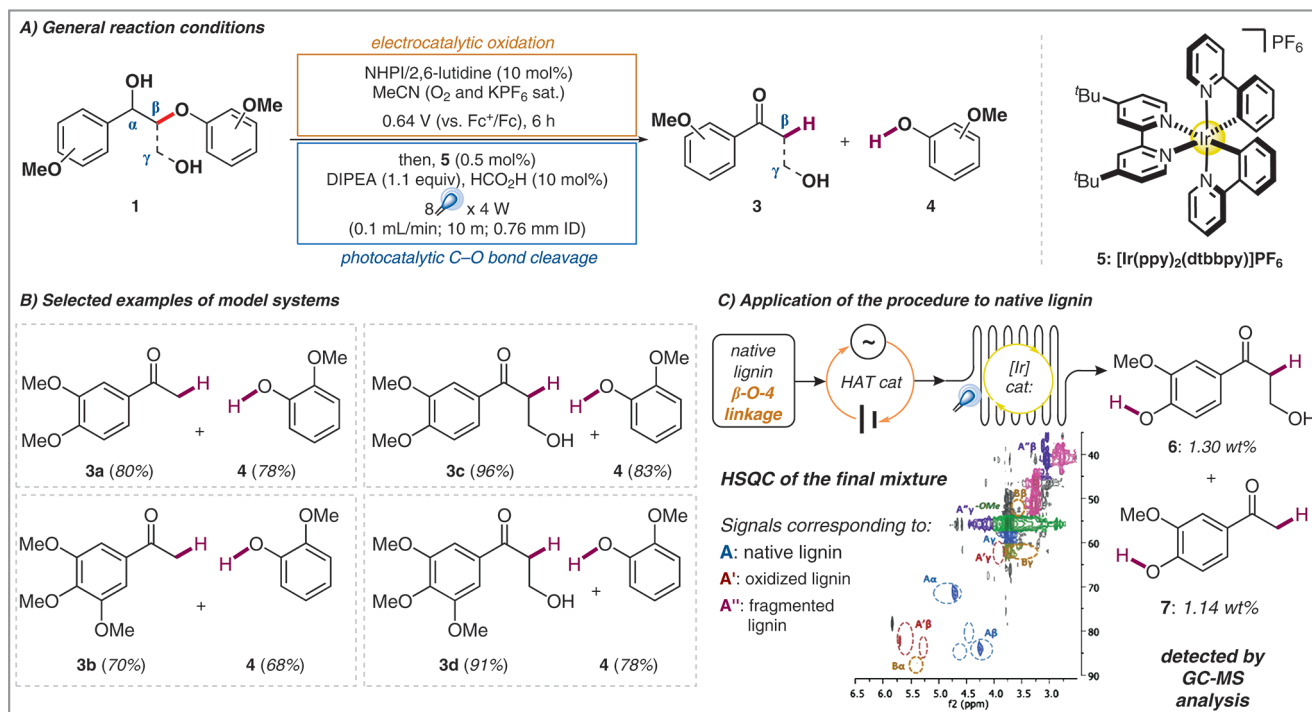
Surprisingly, the compatibility of the catalytic electrochemical oxidation with the group's previously reported photocatalytic fragmentation methodology was exceptional and the authors were happy to observe that no further optimization was required. Furthermore, they did not even need any work-up after the oxidation in order to perform the subsequent photocatalytic fragmentation. “Indeed, we decided to carry out the fragmentation in flow to further prove the robustness of the process and to shorten the reaction times since batch fragmentation would have required 12 hours, as opposed to flow where the fragmentation products were obtained after only 3–4 hours,” said Professor Stephenson. “In addition, industry has gained an increased interest in flow technologies due to their notable advantages where photocatalysis is one of the fields that has extensively proved to be superior,” he added. “With the optimized conditions (Scheme 2, A), the submission of the different model systems to the electrocatalytic oxidation/flow photocatalytic fragmentation in a one-pot fashion gave the corresponding fragmentation products in good yields (Scheme 2, B). Note that room temperature is used in both steps of the process, which is a remarkable advantage from the previously reported methodologies.”

Professor Stephenson revealed that the group started this project with the ultimate goal of making a real difference from known methodologies and, ideally, having an impact on the

lignin processing industry, in pilot or even on industrial scale. “Moving from models to real systems is not always trivial and most of the time – if not every time – it requires careful re-optimization of the process. For this reason, we decided not to simply keep our results to model systems, but to extend the use of our procedure to the fragmentation of isolated native lignin,” said Professor Stephenson.

As expected, moving from a model system to a native lignin proved to be challenging, and all of the group's initial attempts subjecting isolated lignin to the optimized one-pot process failed. “Soon we realized that we needed to find new conditions for the electrocatalytic oxidation as the isolated lignin was completely insoluble in MeCN,” explained Professor Stephenson. He continued: “We evaluated compatible solvent mixtures but none of the evaluated combinations were successful. We even tried to re-optimize the selected electrolyte and the concentration of all the components, but all attempts failed. Looking in the literature, we came across a purification procedure that we applied to our native lignin, which increased the solubility of the lignin by removal of some insoluble impurities, and after several attempts, we were able to obtain a homogeneous reaction mixture using an acetone–DMSO (98:2) solvent combination. After this small alteration, the reaction profile completely changed and we were able to detect the oxidation of the lignin through heteronuclear single quantum coherence spectroscopy (HSQC) analysis.” Taking advantage of the homogeneity of the oxidized reaction mixture, the flow fragmentation occurred smoothly as observed by HSQC analysis of the product mixture. GC-MS traces of this final mixture revealed the presence of the monomeric units **6** and **7**, fragments that have the same nature as the ones observed from the fragmentation of the model systems (Scheme 2, C). “Remarkably, no other types of monomers were detected, which highlights the selectivity of this procedure towards the oxidation of the benzylic alcohol of the β–O–4 linkage versus the pendant primary alcohol,” said Professor Stephenson.

“So far, this procedure has proven to be highly sensitive in our hands when using different batches of native lignin regarding the electrocatalytic oxidation step, which switches off the moment the reaction mixture becomes slightly heterogeneous,” continued Professor Stephenson, adding: “We believe that this is a consequence of the presence of small impurities in the native lignin. We are conscious that this restriction currently limits the potential use of the developed methodology on larger scales because the lignin obtained from industrial processing does not have the same purity required for this procedure.” Professor Stephenson believes that although hitherto undiscussed, these challenges faced



Scheme 2 Summary of the most relevant results. A) General optimized reaction conditions; B) Selected examples of dimeric model systems; C) Selected results of the application of the procedure to native lignin isolated from pine shavings. NHPI: *N*-hydroxyphthalimide; DIPEA: diisopropylethylamine; HAT: hydrogen atom transfer; ID: internal diameter. Adapted with permission from *ACS Cent. Sci.* **2017**, *3*, 621–628, DOI: 10.1021/acscentsci.7b00140, Copyright 2017 American Chemical Society.

in process-scale valorization of lignin may act as a call-to-action for innovations in lignin extraction methods, which are mainly responsible for impurities and functional group manipulations that may impede known chemical processes. “In addition, electrocatalysis of organic processes is not fully implemented in industry because of the intrinsic increased resistance that a non-aqueous electrochemical cell possesses on large scale,” said Professor Stephenson. “However, we hope that the notable advantages of electrocatalytic versus chemical processes will soon be recognized and further resources will be aimed to achieve more efficient organic electrochemical transformations on large scale. In addition, since the photocatalytic step in this procedure proved to be efficient in flow, we believe that further investment in flow electrocatalytic cells that avoid the use of electrolytes will be compatible with our procedure,” added Professor Stephenson. He concluded: “Ideally, we can envision that a complete flow process at notably mild reaction conditions at room temperature could ultimately be realized in a not-too-distant future to provide aromatic commodity chemicals from lignin.”

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