

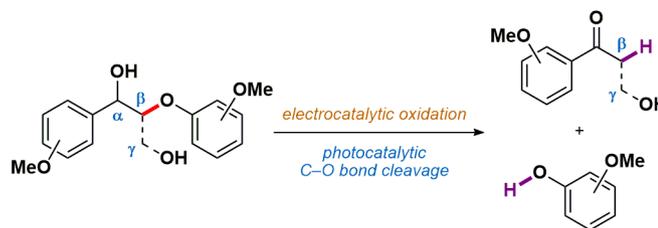
# Synform

People, Trends and Views in Chemical Synthesis

2017/11

## Redox Catalysis Facilitates Lignin Depolymerization

Highlighted article by I. Bosque, G. Magallanes,  
M. Rigoulet, M. D. Kärkäs, C. R. J. Stephenson



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## Dear Readers,

It's nearly Halloween but this new number of SYNFORM is all but spooky: no ghosts, no vampires, no monsters, just the usual poker of articles covering some of the best scientific articles that appeared in the recent organic chemistry literature.

Let's have a glimpse at the content of this November issue then. David Barker's (New Zealand) total synthesis of Ovafofinins A and B achieved through a cascade cyclization is a very rich entry, followed by a Young Career Focus interview to Jianhui Huang (P. R. of China) who gives an excellent presentation of his scientific interests and achievements so far. The third contribution reports on a ground-breaking new methodology allowing the direct use of nitroarenes – without having to convert them into aryl halides – as substrates for the Suzuki–Miyaura cross-coupling. The fourth and final article covers a new method for depolymerizing lignin into useful building blocks via redox catalysis.

That's all for November and let's go home now, it's almost dark outside, and quite foggy too. Wait. Did you hear that noise, like a creaking door? Right, no worries, perhaps is just the wind. Actually, must be the wind. Again that noise... did you hear it now? And now like a maniacal laughter? The corridors of the Institute are plunged into darkness; there should be nobody around on a Saturday evening... Oh well, I think I know what it is... it must be my colleague who has got his paper rejected once again by that super high impact factor journal... right now he is probably transforming into Mr. Hyde again, he should have followed my advice to submit his paper to either SYNLETT or SYNTHESIS... at least he doesn't need a costume for Halloween... Mwahahaha...

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Enjoy your reading and remember: follow us on Twitter! Mwahahaha...



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If you have any questions or wish to send feedback, please write to Matteo Zanda at: [synform@outlook.com](mailto:synform@outlook.com)

## Total Synthesis of Ovafolinins A and B: Unique Polycyclic Benzoxepin Lignans through a Cascade Cyclization

*Angew. Chem. Int. Ed.* **2017**, *56*, 9483–9486

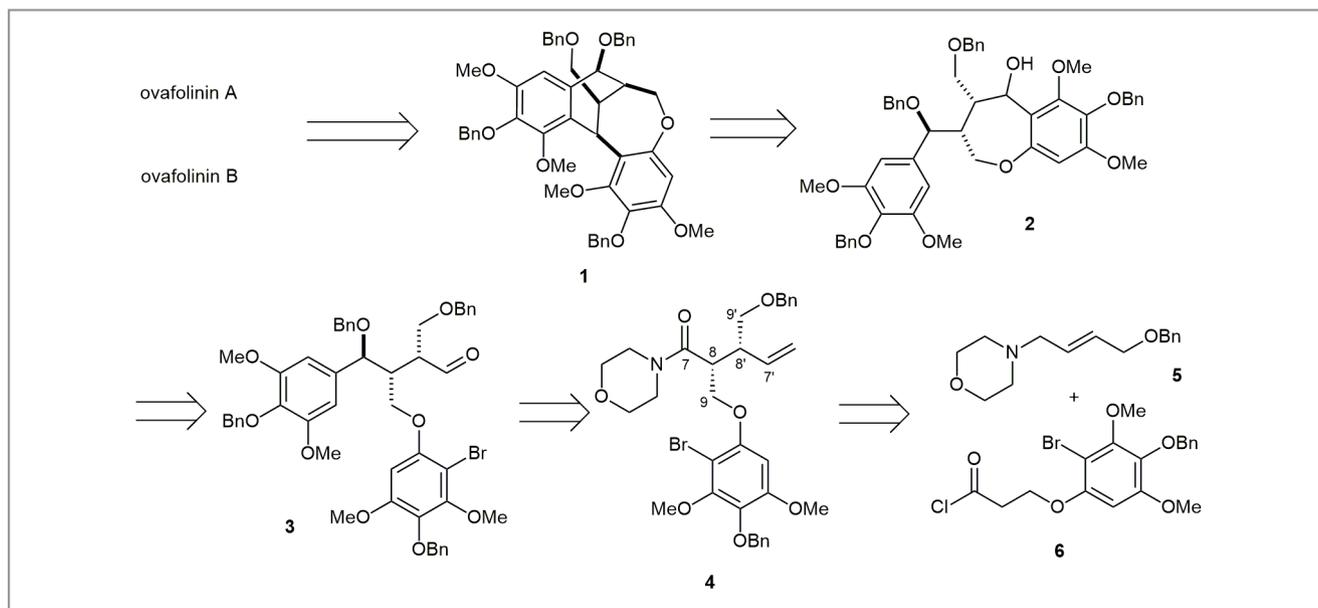
Since 2009, the research group of Professor David Barker at the University of Auckland (New Zealand) has been interested in the use of the acyl-Claisen rearrangement and its application to the synthesis of lignan natural products. Professor Barker said: “We have previously used this approach to synthesise a number of different lignan subclasses including tetrahydrofuran lignans such as galbelgin<sup>1</sup> and magnosalicin,<sup>2</sup> diarylbutanol lignans (kadangustin J<sup>3</sup>) and aryl tetralin lignans (such as cyclogalgravin<sup>1</sup> and isoguaiacin<sup>4</sup>).”

He continued: “In this case we wished to demonstrate the utilisation of these strategies in a complex example. Ovafolinins A and B represent unique structural targets as they are the only examples of lignan natural products containing a seven-membered benzoxepin penta- or tetracyclic scaffold, respectively. This would allow us to determine the power and utility of our approach to complex natural products.” The group began the synthesis in 2014 by developing a retrosynthetic plan which aimed to form the six-membered tetrahydronaphthalene ring of the polycyclic structure **1** after the seven-membered benzoxepin ring in **2** (Scheme 1). “The rationale for this approach was that the seven-membered ring

could be formed through an intramolecular cyclisation of an open-chain precursor **3** more easily at this stage rather than trying to form it in a constrained tricyclic molecule,” explained Professor Barker. The open-chain precursor **3** would be accessed from an acyl-Claisen derived amide **4**, synthesised from a substituted allylic morpholine **5** and  $\beta$ -phenoxy acid chloride **6**.

The synthetic steps to prepare **5** and **6** worked very well, as the group expected, giving them the required starting materials to attempt the acyl-Claisen rearrangement. “Unfortunately, we were to discover that the main isolated product from this reaction was a substituted acrylate, which we thought was a very complicated and redundant way to form such compounds,” commented Professor Barker. He continued: “Further model studies showed that all acid chlorides containing a  $\beta$ -alkoxy group underwent the same unwanted reactions and did not undergo the acyl-Claisen reaction. This led us to redesign our synthesis, still utilising the acyl-Claisen rearrangement but altering the reaction substrates.”

In the group’s initial approach, the mapping of carbons of the final structures onto amide **4** would be as shown in

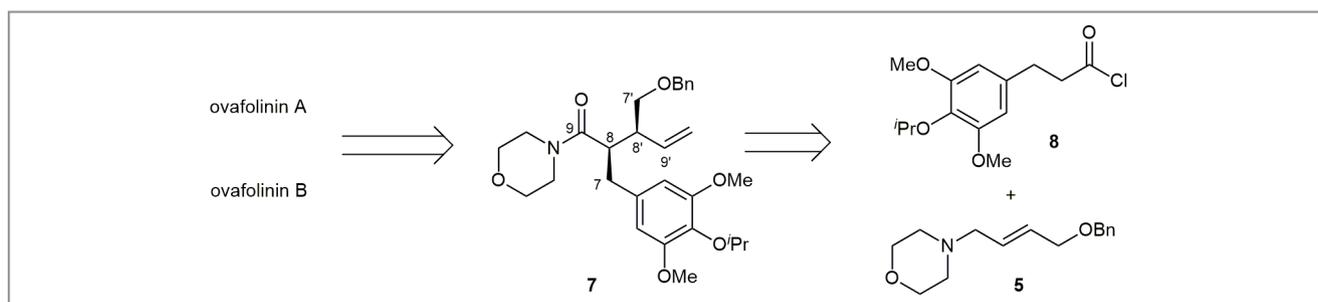


**Scheme 1** Initial retrosynthetic approach to ovafolinins A and B

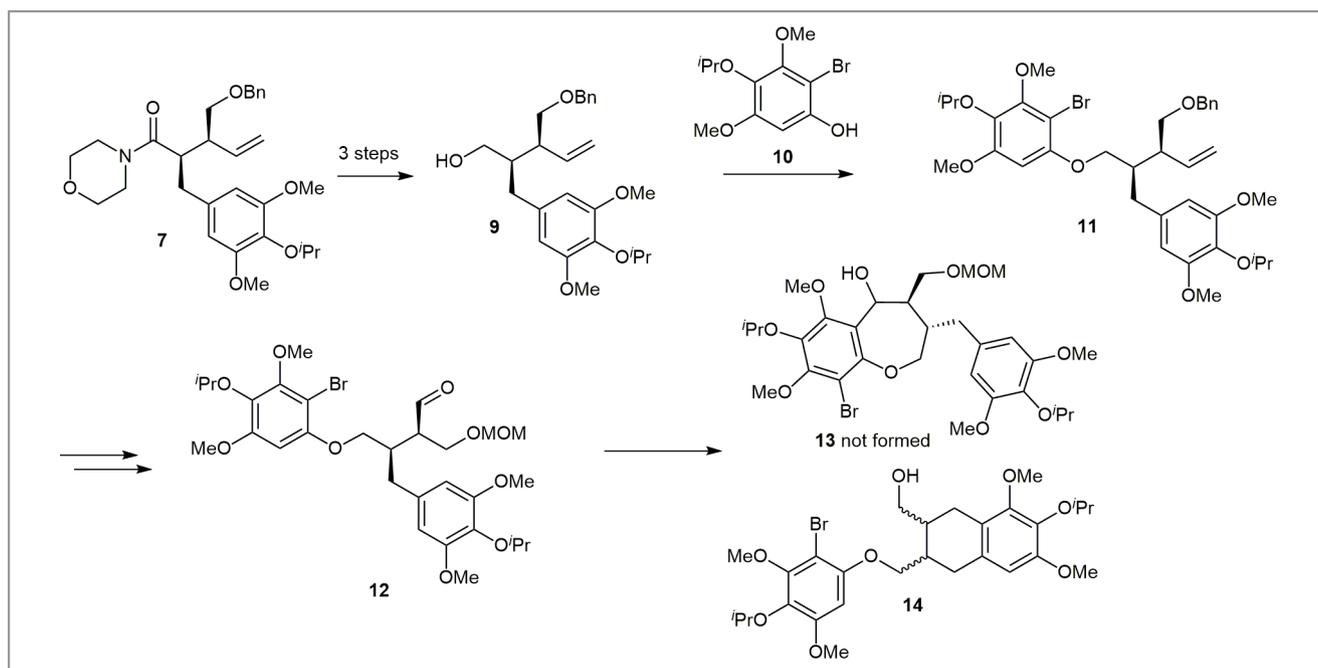
Scheme 1. “We envisaged that it would be possible to remove the troublesome  $\beta$ -alkoxy fragment (C-8 to C-9) and instead form amide **7** (Scheme 2), which contains a substituted benzyl group at C-8,” said Professor Barker. “This would require that the amide would eventually become C-9 in the final compounds. Additionally, because of this interconversion, the original mapping of C-7' and C-9' would be swapped to retain the same relative stereochemistry. We envisaged, based on our previous experience with this reaction,<sup>5,6</sup> that it would be much easier to form amide **7** from **5** and newly prepared acid chloride **8**.”

Synthesis of acid chloride **8** was easily achieved from syringaldehyde and the authors of this study were pleased to find that its acyl-Claisen rearrangement with amine **5**

proceeded to give the desired amide **7** in almost quantitative yields as a single diastereoisomer. Professor Barker said: “Conversion of the amide group in **7** into the desired primary alcohol **9** was achieved over three steps (iodolactonisation, reductive ring opening and finally reduction of the carboxylic acid) using a strategy we have previously used (Scheme 3).<sup>7</sup> Mitsunobu reaction of phenol **10** (which was also prepared from syringaldehyde) and alcohol **9** gave ether **11**, which had then effectively added the phenoxyethyl moiety which could not be accessed via our original acyl-Claisen route. Oxidation/periodate cleavage followed by reduction of the alkene in **11** gave a primary alcohol, which was initially protected as a MOM ether. We chose this protecting group as we have previously found it to be highly compatible with our lignan



**Scheme 2** Revised retrosynthetic approach to ovafolinins A and B



**Scheme 3** Attempted synthesis of benzoxepin **13**

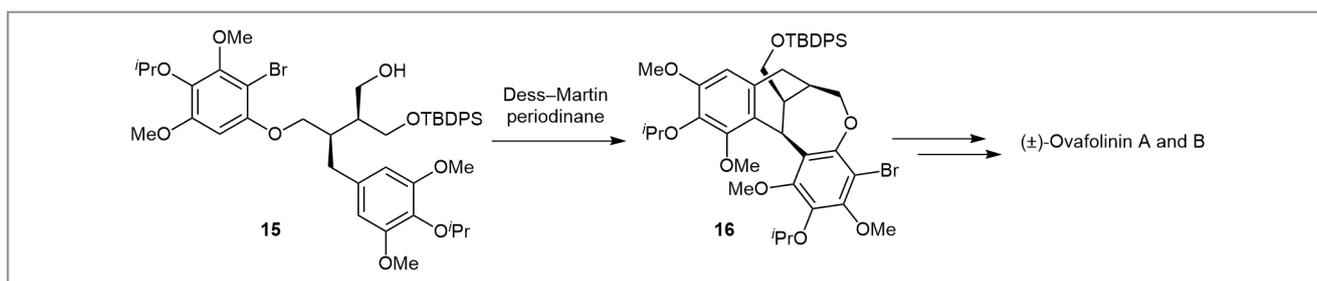
syntheses, as generally there is an acid-catalysed step during which the MOM group is removed, effectively reducing the synthesis by one step. Unfortunately we were to discover that in this case the MOM group in aldehyde **12** was incompatible with the intramolecular cyclisation step to form the seven-membered benzoxepin **13**, with tetrahydronaphthalene **14** being the only compound obtained in appreciable amounts. This led us to investigate this process using molecular modelling where we found that if a protecting group larger than a MOM was used, it appeared that the aryl bromide and aldehyde functionalities would be in very close proximity which we believed would help facilitate the desired cyclisation.”

It was then decided to use a large TBDPS protecting group, which gave the theoretical best geometry between the two reactive sites. After preparation of the TBDPS-protected cyclisation precursor, alcohol **15**, the group expected that its oxidation would give the corresponding aldehyde, ready to test their cyclisation theory (Scheme 4). Professor Barker revealed: “However, we were delighted to find that under the oxidation conditions we did not obtain the aldehyde but instead, fortuitously, the tetracyclic framework of ovafolinin B (**16**). This was a pleasant surprise but highlights the highly electron-rich nature of these compounds and shows that if the reactive groups are placed in the correct orientation then these lignan-like molecules are formed in a biosynthetic-like manner. This was further seen when, upon removal of the protecting groups from **16**, not only was ovafolinin B formed, but also the formation of the final tetrahydrofuran ring was induced to give ovafolinin A. After all the challenges of setting up the linear precursors for these compounds, we were very happy to have these key ring-forming steps occurring so readily and under such mild conditions.”

Following this, the group embarked on an enantioselective synthesis of ovafolinins A and B. Professor Barker explained that there are no existing relevant examples of asymmetric acyl-Claisen reactions, with the only well-studied examples requiring  $\alpha$ -alkoxy groups which unfortunately were not ap-

plicable to this synthesis.<sup>8</sup> “We tried a number of different approaches to asymmetrically prepare the debromo analogue of linear precursor **15**, many of which were unsuccessful. Finally, we resolved this by using a route based on an Evans asymmetric alkylation,” said Professor Barker. He continued: “Luckily, the approach worked well, with the only problem being the selective functionalisation of the diol (compound **28** in the paper) where all efforts to efficiently monosilylate it gave an inseparable mixture of regioisomers.” Fortunately, the Auckland-based researchers were able to separate the desired isomer after the Mitsunobu reaction. “This gave us our linear precursor as a single enantiomer which was then successfully converted into (+)-ovafolinins A and B,” said Professor Barker. The natural products had originally been assigned their absolute stereochemistry based on their CD (circular dichroism)<sup>9,10</sup> spectra; however, the synthesis showed that the assignment was incorrect. “This is not the first time we have discovered that the use of CD to assign absolute stereochemistry in lignan natural products has led to an incorrect assignment,<sup>11</sup>” remarked Professor Barker. “We believe that in many cases it is the fact that the CD spectra of these natural products are compared to those of highly simplified compounds that leads to these incorrect assignments, which unfortunately is routinely used on this class of natural products.”

When the optical rotation values of the synthetic compounds were analysed and compared to the natural ones, the group was intrigued to see that their compounds had a significantly higher magnitude of rotation and that the natural compounds had been reported with opposite signs. “As our synthesis showed that these natural products are easily interconverted, we would have expected them to have the same sign of rotation like our synthetic samples,” explained Professor Barker. The NMR spectra of the originally isolated natural products did not suggest the presence of other impurities which could have altered the optical rotation. Therefore, to account for the differences in rotation, the group postulated that the natural compounds are derived from a racemic pre-



**Scheme 4** Final steps to (±)-ovafolinins A and B

cursor, potentially ovafolinin B, one enantiomer of which may have been preferentially oxidised to ovafolinin A. This could account for the apparently scalemic nature of the natural products and their opposite signs.

“This work has highlighted the acyl-Claisen rearrangement as a powerful synthetic tool to prepare complex structures with its high level of diastereoselectivity combined with its ease of modifying the substituents being key advantages,” said Professor Barker, continuing: “In the end it was our insightful analysis of the products during the MOM-protected synthesis that led us to the critical finding that the linear precursor could be coaxed into a reactive conformation by use of an alternate protecting group. Without the molecular modelling we may just have easily embarked on a different synthetic route which may or may not have eventually been successful.” He concluded: “We aim now to use this approach to form other members and analogues of the ovafolinin family as well utilising these methods for the synthesis of other complex natural products.”

*Mattias Farnok*

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## About the authors



Prof. D. Barker

**David Barker** was born in Altrincham (UK). After moving to Australia, he graduated from the University of Sydney (Australia) with a BSc degree (Honours, First Class) and then completed his PhD in 2002 at the same university. After postdoctoral research at the School of Medical Sciences at the University of New South Wales (Australia), he joined the University of Auckland (New Zealand) as a lecturer. He is currently an Associate Professor in Organic and Medicinal Chemistry and he has a diverse range of synthetic interests including biologically active natural products, drug discovery, and development of novel polymeric scaffolds.



S. J. Davidson

**Samuel J. Davidson** was born in Auckland (New Zealand). He graduated in 2012 from the University of Auckland (New Zealand) with a BSc in medicinal chemistry. Samuel then went on to graduate with a BSc (Honours, First Class) in 2013. He is currently completing his PhD at the same university under the supervision of Associate Professor David Barker.

## Young Career Focus: Professor Jianhui Huang (Tianjin University, P. R. of China)

**Background and Purpose.** SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Jianhui Huang (Tianjin University, P. R. of China).

### Biographical Sketch



Prof. J. Huang

**Jianhui Huang** is from Tianjin (P. R. of China). He received his B.A. degree in analytical chemistry from Hu'nan University (P. R. of China) in 2000. He decided to study abroad in 2003 and received his Ph.D. in chemistry from the University of York (UK) under the guidance of Professor Peter A. O'Brien. In 2007, he moved to the University of Sheffield (UK) working with Professor Joseph P. A. Harrity on the cycloaddition reactions of alkynyl boronates. He started his independent research in 2010 when he returned to China and joined the faculty as an Associate Professor of Medicinal Chemistry in the School of Pharmaceutical Science and Technology at Tianjin University (P. R. of China).

His research interest covers the development of new synthetic tools and design/synthesis of useful metal-containing scaffolds for medical purposes. Other interests include entertaining his daughter Agnes and pipe making.

### INTERVIEW

**SYNFORM** *What is the focus of your current research activity?*

**Prof. J. Huang** The research focus of our group is to develop new disruptive ways of molecular modification/construction. In particular, we are currently focusing on the development of strategies for the preparation of reliable molecular scaffolds using metal as the core element.

**SYNFORM** *When did you get interested in synthesis?*

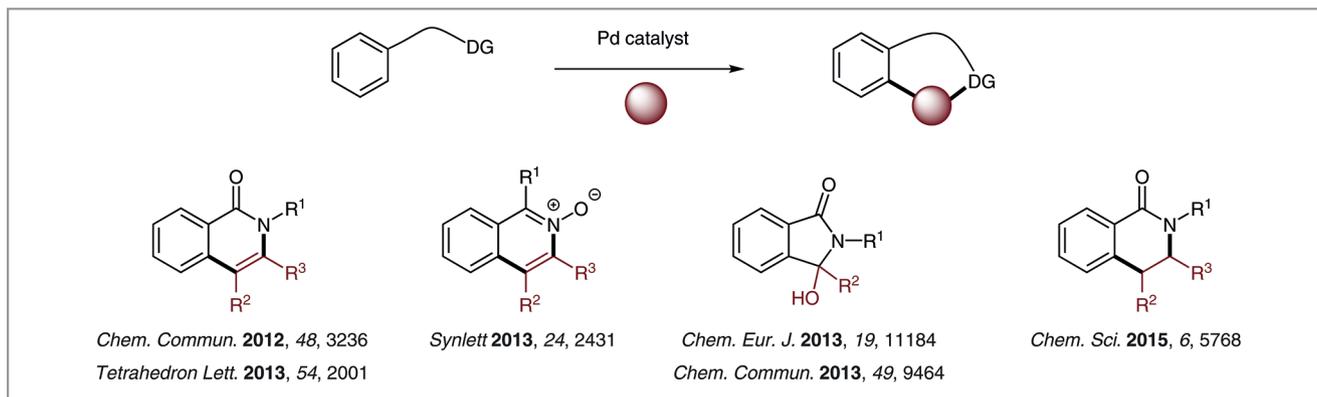
**Prof. J. Huang** When I first worked at Tianjin Institute of Pharmaceutical Research (P. R. of China), we were working on the development of new processes for generic drugs. I found the real chemical world is a little different from what we know from the textbook and practical course. It is challenging and rewarding! I started working in the unknown world tasting the flavor of discovery.

**SYNFORM** *What do you think about the modern role and prospects of organic synthesis?*

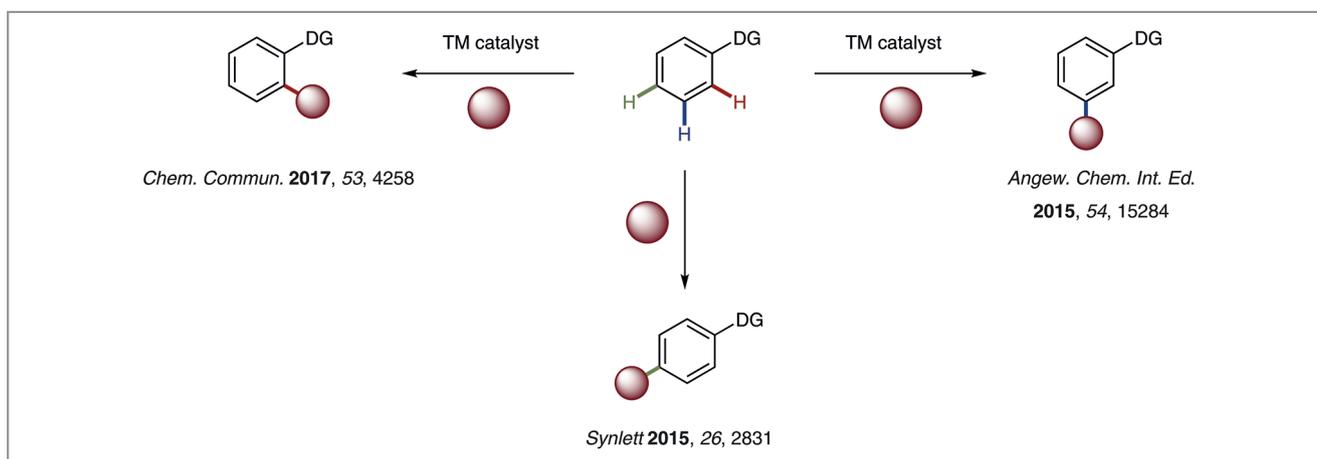
**Prof. J. Huang** I think we will have to expand the chemical space with the increase of molecular complexity!!! We have been a little conservative on the conventional molecules, avoiding technical problems. Challenges need be taken on both molecular science (design/synthesis) and molecular engineering (separation/characterization).

**SYNFORM** *Your research group is active in the area of synthetic methodology and bioorganic/medicinal chemistry. Could you tell us more about your research and its aims?*

**Prof. J. Huang** We have developed a number of new strategies for the construction of heterocycles through a number



**Scheme 1** Pd-catalyzed synthesis of various heterocycles via C–H activation



**Scheme 2** Selective arene functionalization

of key transition-metal-catalyzed C–H activation annulation reactions. These methods were successfully applied to the synthesis of isoquinolones,<sup>1</sup> isoindolones<sup>2</sup> and tetrahydroisoquinolones<sup>3</sup> (Scheme 1).

Our aims are simply to make compounds by late-stage functional group introductions to design and create molecules covering new chemical spaces, in particular, the preparation of stable organometallic/inorganic drug-like molecules (a major part of our current research focus).

**SYNFORM** What is your most important scientific achievement to date and why?

**Prof. J. Huang** We have focused on regioselective arene functionalizations. More specifically, we were able to promote a meta-selective bromination of arenes using ruthenium catalysis (Scheme 2),<sup>4</sup> These approaches have provided new tools for molecular design in much more efficient ways.

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*Matthew Farnock*

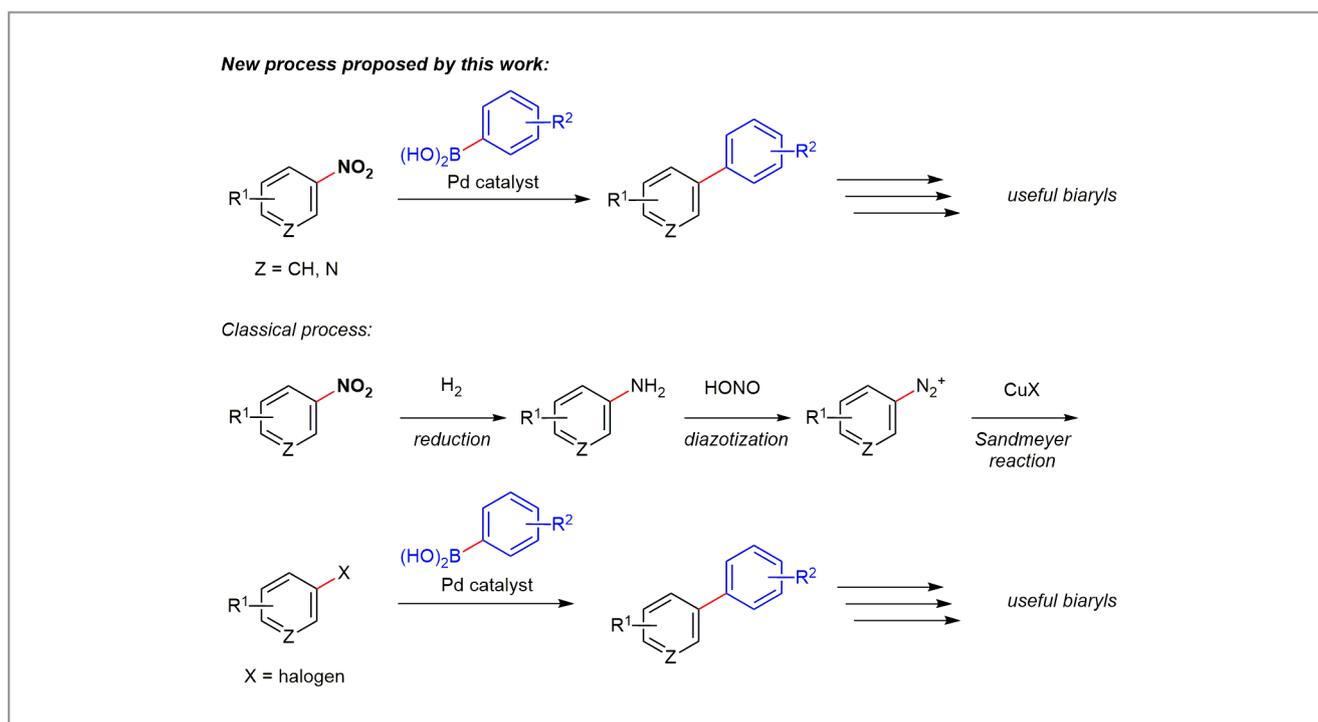
## The Suzuki–Miyaura Coupling of Nitroarenes

*J. Am. Chem. Soc.* **2017**, *139*, 9423–9426

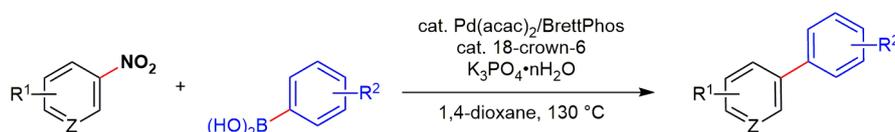
The Suzuki–Miyaura cross-coupling reaction is an indispensable synthetic tool for modern organic synthesis to assemble biaryls, which are ubiquitous in useful substances such as pharmaceuticals, agrochemicals, and materials. One avenue of ongoing research to improve the practicality of the transformation is to seek aryl electrophiles alternative to aryl halides to avoid halogen contaminations in products and wastes as well as to streamline and diversify chemical processes to access biaryls. While many different aryl electrophiles such as aryl esters, aryl ethers, aryl carboxylic acid derivatives, and aryl ammonium salts have been introduced for the Suzuki–Miyaura cross-coupling in the last decade, no successful report has been available for the use of nitroarenes as the coupling partner. Recently, a research endeavor led by Professor Shigeyoshi Sakaki (Fukui Institute for Fundamental Chemistry, Kyoto University, Japan) and Professor Yoshiaki Nakao (Kyoto University, Japan) showed for the first time that nitroarenes can be viable aryl electrophiles for the Suzuki–Miyaura cross-coupling reaction. “Nitroarenes are common

synthetic building blocks in chemical processes and often serve as starting materials to derivatize aromatic compounds because nitration is one of the most reliable and established methods to functionalize arenes,” said Professor Nakao. Classical processes involving nitration followed by reduction, diazotization, and the Sandmeyer reaction are still running in the chemical industry. “For this reason, the use of nitroarenes for the cross-coupling chemistry is highly desirable because the method could exclude the classical multi-step processes to functionalize arenes (Scheme 1),” said Mr. Takanori Miyazaki from the TOSOH corporation, one of the co-authors of this work.

“We have come up with very simple reaction conditions employing Buchwald’s BrettPhos as a key ligand to enable the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of nitroarenes (Scheme 2),” explained Mr. Miyazaki. He continued: “The reaction requires a relatively higher temperature compared to the cross-couplings of aryl halides due to reluctant oxidative addition of the C–NO<sub>2</sub> bond of nitroarenes, but



**Scheme 1** Comparison of chemical processes to access biaryls starting from nitroarenes



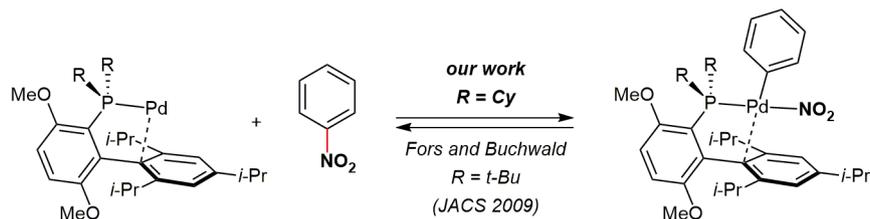
**Scheme 2** The Suzuki–Miyaura cross-coupling of nitroarenes

no exotic or complex reagents or conditions have been utilized to achieve the new reaction. We indeed planned to develop this reaction as a user-friendly process as we knew the potential value of the methodology, if available.” Never imagining that standard cross-coupling conditions would work, and since many papers had already been published showing that nitroarenes are poor substrates for the reaction, one of the other authors, Dr. M. Ramu Yadav, started to screen more sophisticated systems such as the use of other transition metals and multiple metal catalysts to tackle the reaction.

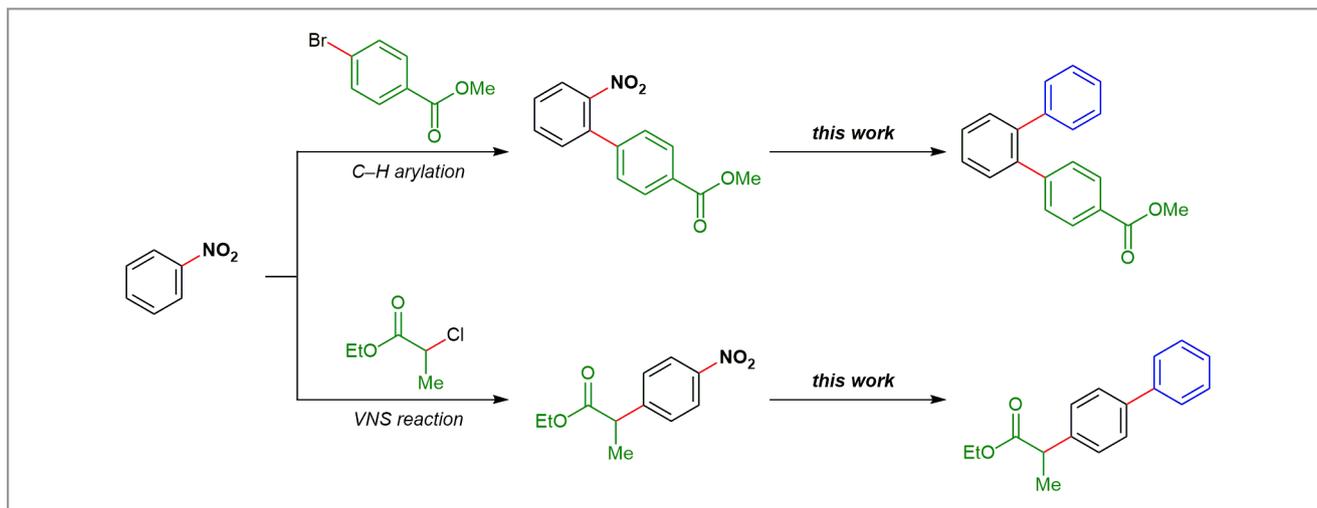
“There was actually a key finding available in the literature, previously described by the Fors and Buchwald group, who reported the nitration of aryl halides by palladium/*t*-Bu-BrettPhos catalysis (*J. Am. Chem. Soc.* **2009**, *131*, 12898),” said Professor Nakao. “In that reaction – which is the reverse reaction of the desired oxidative addition of Ar–NO<sub>2</sub> (Scheme 3) – the reductive elimination of the Ar–NO<sub>2</sub> bond via the intermediate palladium complex is a product-forming step, whereas in our case it is a key elemental step of the cross-coupling, as experimentally probed by Dr. Nagaoka.” He continued: “It is interesting to note that the cleavage/formation equilibrium of the Ar–NO<sub>2</sub> bond may be controlled by a subtle change (Cy or *t*-Bu) of the phosphorus ligands, BrettPhos or *t*-Bu-BrettPhos (Scheme 3). This aspect is currently under theoretical investigation by Professor Sakaki and Dr. Zhong, who have revealed a full catalytic cycle of the Suzuki–Miyaura cross-coupling of nitroarenes using calculations supported by some experimental work executed by Dr. Nagaoka, Mr. Kashihara, and myself.”

Calculations as well as catalytic and stoichiometric experimental mechanistic studies demonstrated that the rate-determining step of the reaction was the oxidative addition step. Professor Nakao explained: “The design of novel metal catalysts will probably be necessary to improve the efficiency of this new bond-activation process, which in turn would lead to an improved overall utility of the new nitroarene-based cross-coupling reaction. This would also likely lead to the possibility of using a greater diversity of nucleophilic coupling partners, in line with the rich chemistry demonstrated in many previous aryl halide based cross-coupling studies.”

“Nitroarenes feature a unique reactivity due to the strongly electron-withdrawing nature of the nitro group. For example, *ortho*- and *para*-positions of nitrobenzene can be directly functionalized to install organic substituents via C–H arylation and vicarious nucleophilic substitution (VNS) reactions, respectively,” remarked Professor Nakao. He concluded: “Subsequently, the nitro group can be submitted to the coupling reaction developed in this study, enabling the synthesis of disubstituted benzenes (Scheme 4).”



**Scheme 3** Oxidative addition/reductive elimination of the Ar–NO<sub>2</sub> bond by Pd/BrettPhos complexes



**Scheme 4** Synthesis of disubstituted benzenes through C–H functionalization and the Suzuki–Miyaura coupling reactions of nitrobenzene

Mattias Fenske

## About the authors



From left: Dr. M. R. Yadav, Dr. M. Nagaoka, M. Kashihara

**M. Ramu Yadav** obtained his Ph.D. degree working on metal-catalyzed C–H functionalization of arenes at the University of Hyderabad (India) under the supervision of Professor Akhila K. Sahoo in 2014. He has been a postdoctoral researcher at Kyoto University (Japan) with Professor Yoshiaki Nakao since 2015.

**Masahiro Nagaoka** obtained his Ph.D. degree working on the synthesis and reactivity of polyhydrido metal clusters under the supervision of Professors Hiroharu Suzuki and Toshiro Takao in 2016 at Tokyo Institute of Technology (Japan). He then joined the research group of Professor Yoshiaki Nakao as a postdoctoral fellow. He is currently a research scientist at Sagami Chemical Research Institute (Japan).

**Myuto Kashihara** obtained his B.S. degree at Kyoto University (Japan) in 2017 and has just started his graduate study in the group of Professor Yoshiaki Nakao.



T. Miyazaki

**Takanori Miyazaki** obtained his M.S. degree at Kyushu University (Japan) in 2004. He is currently a senior researcher at TOSOH corporation. He is collaborating with the group of Professor Nakao to develop the new reaction described here and hoping that the novel transformation of nitroarenes will expand.



From left: Prof. S. Sasaki, Dr. R.-L. Zhong

**Shigeyoshi Sakaki** (Ph.D.; Professor Emeritus) has been a senior research fellow in the Fukui Institute for Fundamental Chemistry, Kyoto University (Japan) since his retirement from a full professor position at Kyoto University. He is working in the theoretical and computational chemistry of d element(s) with much interest in the reaction mechanism of organometallic and catalytic reactions.

**Rong-Lin Zhong** is a lecturer at the Institute of Theoretical Chemistry, Jilin University (P. R. of China). He obtained his B.S. degree from Northeast Normal University (P. R. of China) in 2010. He then joined Professor Zhong-Min Su's group in Northeast Normal University and obtained his Ph.D. degree in physical chemistry in 2015. He has worked in Professor Sakaki's group as a research fellow in the Fukui Institute for Fundamental Chemistry, Kyoto University (Japan) since 2016.



Prof. Y. Nakao

**Yoshiaki Nakao** was educated in chemistry at Kyoto University (Japan; Ph.D. with Professors Tamejiro Hiyama and Eiji Shirakawa), Yale University (USA; visiting student with Professor John F. Hartwig), and the Max-Planck-Institut für Kohlenforschung (Germany; visiting scholar with Professor Manfred T. Reetz). He was appointed as an assistant professor at Kyoto University in 2002, and has been a full professor since 2014. He is interested in developing new synthetic reactions by catalysis.

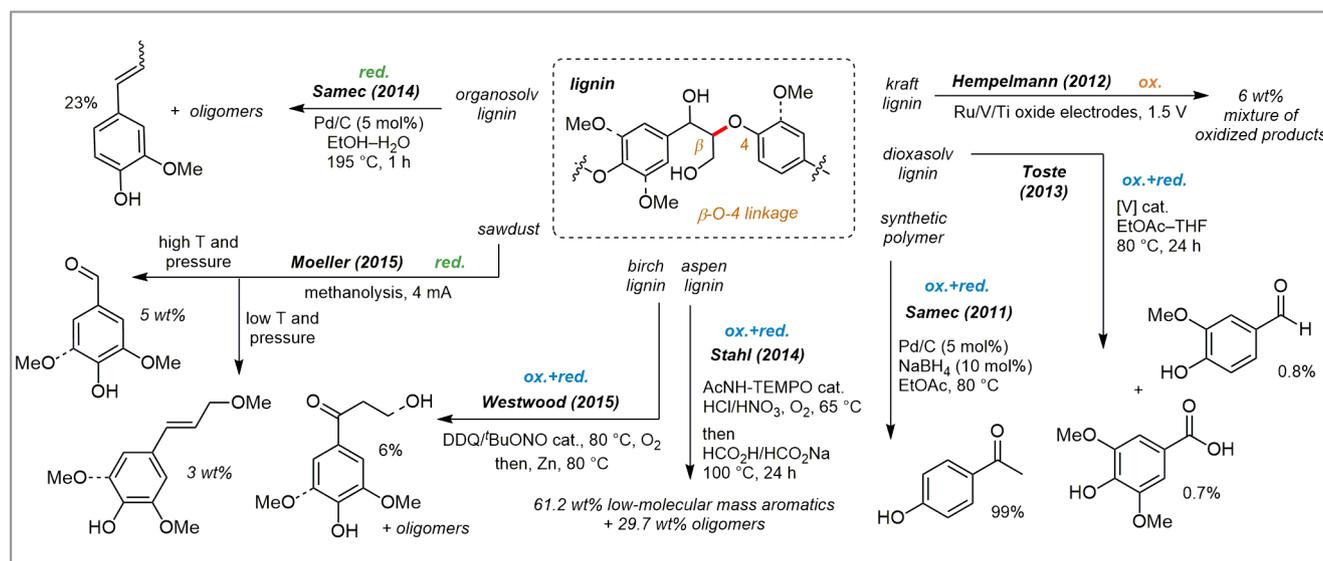
## Redox Catalysis Facilitates Lignin Depolymerization

*ACS Cent. Sci.* **2017**, *3*, 621–628

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  $\beta$ -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 NaClO<sub>4</sub>, a common electrolyte, only when the three components were present. This result clearly indicated the non-innocent role of the NaClO<sub>4</sub> electrolyte in our reaction. Although we have not been able to identify the precise nature of this precipitate, <sup>1</sup>H 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, KPF<sub>6</sub> 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."

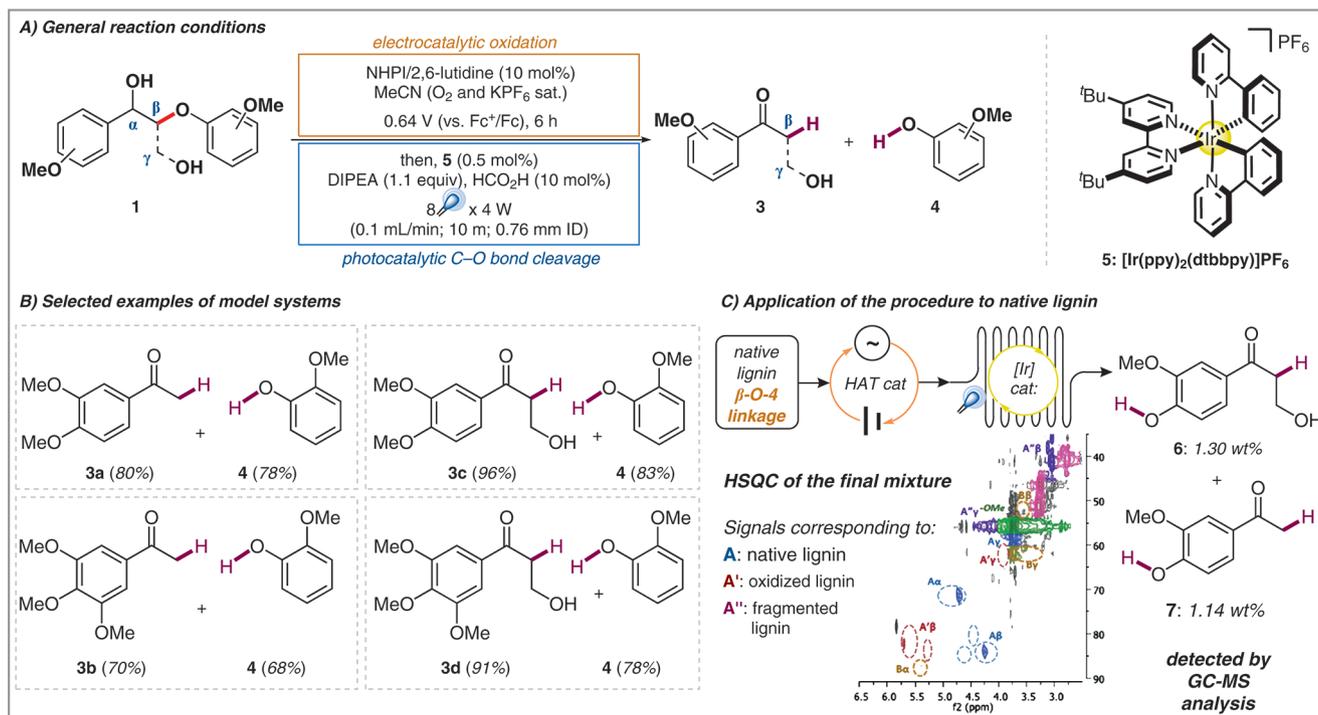
Surprisingly, the compatibility of the catalytic electrochemical oxidation with the group's previously reported photocatalytic fragmentation methodology was exceptional and the authors were happy to observe that no further optimization was required. Furthermore, they did not even need any work-up after 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.”

*Matthews female*

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