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New strategies in organic electrosynthesis: general discussion

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Dylan G. Boucher, Richard C. D. Brown,  Victoria Flexer, 
Robert Francke,  Bernardo Antonio Frontana-Uribe, 
Seyyedamirhossein Hosseini,  Long Luo,  Shelley D. Minter, 
Robert Price,  Naoki Shida,  Jose Manuel Ramos-Villaseñor 
and Thomas Wirth 

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Robert Francke opened a general discussion of the paper by Bernardo Antonio Frontana-Uribe: The plot of the ionic conductivity vs. the supporting electrolyte concentration in your paper (<https://doi.org/10.1039/d3fd00064h>), appears to follow a discontinuous function in cyrene–EtOH (1 : 1). How can this unusual behavior be explained?

Bernardo Antonio Frontana-Uribe answered: A possible explanation is that the intermolecular aggregations of the cyrene–EtOH solvent mixture allow the dissociation of a greater amount of supporting electrolyte, increasing the conductivity. But further studies are required to clarify this hypothesis.

Robert Francke suggested: The behavior of the cyrene–EtOH-based electrolyte solutions in the conductivity measurements is very interesting. Molecular dynamics simulations could be taken into consideration for a better understanding of the unusual properties.

Bernardo Antonio Frontana-Uribe replied: Thanks for the suggestion. Molecular dynamic simulations will be taken into consideration for understanding the possible intermolecular aggregations of cyrene–EtOH solvent mixtures interacting with the supporting electrolyte.

Mickael Avanthay said: The conductivity of the solvent is very low, so it seems it is not suitable to be used on its own. You detail the use of ethanol co-solvent – what is the minimum amount of co-solvent possible, and are other co-solvents appropriate?

Bernardo Antonio Frontana-Uribe responded: We think that the minimum quantity of co-solvent should be 30% ethanol in a cyrene/ethanol mixture, to

avoid conductivity issues. The viscosity value of this solvent mixture is 8.4 cP, which we consider as the limit that does not cause conductivity issues. Using less than 30% of ethanol as co-solvent could lead to conductivity issues. Other co-solvents are also possible such as methanol and propylene carbonate.

Mickael Avanthay addressed Jos e Manuel Ramos-Villase or and Bernardo Antonio Frontana-Urbe: Given the solvent is naturally enantiopure, can you use it as a chiral solvent to perform enantioselective electrochemistry from achiral/ racemic reagents?

Jos e Manuel Ramos-Villase or and Bernardo Antonio Frontana-Urbe answered: It can be used for these purposes. In fact, the cathodic reduction of benzaldehyde using the cyrene–EtOH (1 : 1) solvent mixture afforded the dia-steromeric DL pinacol product in greater proportion than the MESO product. But further studies are required to know the potential of cyrene in asymmetric reactions.

Dylan G. Boucher addressed Jos e Manuel Ramos-Villase or and Bernardo Antonio Frontana-Urbe: What is the mechanism you propose for the differing selectivity in different electrolytes?

Jos e Manuel Ramos-Villase or and Bernardo Antonio Frontana-Urbe replied: The corresponding anion radical formed at the electrode surface is stabilized by the Bu_4N^+ cation present at the electric double layer when cyrene is present at high concentration, this process facilitates the second electron transfer near the electrode surface, yielding the diphenylmethanol derivative. On the other hand, the use of LiClO_4 favors the stabilization of the radical anion of benzophenone through its coordination with the lithium cation, promoting the C–C bond formation and obtaining the pinacol product.

Victoria Flexer commented: The solvent you're presenting shows a certain similarity in its chemical structure to DOL (dioxalane), which is used in lithium– sulfur batteries. In the assembly of these batteries, DOL is most often used in combination with 1,2-dimethoxyethane (DME). Have you considered the possibility of mixing cyrene with DME? I was thinking that the mixture could potentially widen the electrochemical window of the cyrene.

Bernardo Antonio Frontana-Urbe replied: Not for the moment, but we have been exploring other solvent mixtures to form aprotic solvent mixtures with cyrene.

Victoria Flexer said: I'm surprised by the high market price of this solvent, particularly given the raw materials from where it is synthesized. Do you foresee any price decrease in the medium to long term?

Bernardo Antonio Frontana-Urbe responded: Yes, I have heard that there are plans to build a new plant for European consumption. This should decrease this solvent price.¹

Shelley D. Minter highlighted: Your work focuses on undivided cells. Can you use this solvent in a divided cell? Do you know if the common separators (Na on, alkaline exchange membranes, etc.) are stable in this new solvent?

Bernardo Antonio Frontana-Urbe replied: Yes, the solvent mixture can be used in a divided cell. We think that the Na on membrane could be stable in this solvent mixture. We have not used alkaline membranes, but we keep in mind that cyrene has a carbonyl functionality and can undergoes an aldolic reaction itself with inorganic bases. Therefore, alkaline exchange membranes used in alkaline media could promote the aldolic reaction of cyrene.

Thomas Wirth added: The current cost of cyrene is very high (approx. £200/ litre). This is due to the production capacity as there is not yet a large scale manufacturing plant available. It was reported that these are currently being built.¹

The solvent cyrene has a carbonyl and a ketal functionality. How are these functionalities surviving the electrochemical reaction conditions? In combination with EtOH as co-solvent, different reaction might be possible which could degrade the solvent.

¹ <https://renewable-carbon.eu/news/resolute-project-update-a-er-15-years-of-work/>.

Bernardo Antonio Frontana-Urbe answered: Under electrochemical conditions the ketal functionality survives due to DABCO being used as a sacrificial reagent to prevent the degradation of cyrene. In combination with EtOH, it could react with the carbonyl functionality of cyrene affording the corresponding ketal that improves the stability of cyrene. However, a $4 F \text{ mol}^{-1}$ er passing, the cathodic reduction of EtOH produces the corresponding alkoxide that can react with cyrene, providing the enolate of cyrene and promoting the aldol reaction of cyrene itself.

Robert Price said: You mentioned that the viscosity of cyrene poses issues for conductivity of the solution when used as a single solvent, hence the requirement for addition of ethanol as a co-solvent. Have you performed any rheological analyses on the mixtures of cyrene : ethanol? In particular, for the 1 : 1 cyrene : ethanol solution, do you see any evidence of dilatant (shear-thickening), pseudo-plastic (shear-thinning), rheopectic (time-dependent shear-thickening) or thixotropic (time-dependent shear-thinning) behaviour that could impact these solutions in terms of mass transport and conductivity?

Bernardo Antonio Frontana-Urbe answered: We have not performed rheological studies indicating that the solvent mixture behaves as a non-Newtonian uid; however, to answer completely this question further studies are required. We will take them into consideration in future experiments.

Robert Price said: How does the viscosity of the co-solvent mixture vary as a function of cyrene ethanol ratio? Is a 1 : 1 ratio optimal for this electrochemistry and how does it behave, rheologically, over time?

Bernardo Antonio Frontana-Urbe answered: The viscosity of the solvent mixture decreases with an increase in the quantity of ethanol. The cyrene–EtOH 1 : 1 mixture has the viscosity value of 7 cP, representing half the value of pure cyrene. The viscosity value of the solvent mixture did not exhibit any change after one hour.

Belen Batanero opened a general discussion of the papers by Bernardo Antonio Frontana-Urbe: I note the surprising effect of this novelty solvent depending on the electrolyte used. In one case (with R₄NBF₄ as electrolyte) the alcohol is the main product, however the dimer (pinacol) is obtained when benzophenone is reduced with LiClO₄ as the electrolyte. What explanation do you have to explain these results? I wonder about the stability of this acetal (solvent) that should be hydrolyzed under acidic conditions to provide a 1,2-dicarbonyl compound. Did you observe any change in solvent appearance when exposed to oxygen or light? Did you previously deoxygenate the cathodic solution in order to avoid superoxide anion formation (which would probably react with the solvent)?

Bernardo Antonio Frontana-Urbe answered: The anion radical formed at the electrode surface is stabilized by the Bu₄N⁺ cation present at the electric double layer when cyrene is present in an equal or major proportion, this process facilitates the second electron transfer at the electrode surface, yielding the diphenylmethanol derivative. Otherwise, the coordination of the lithium cation with the radical anion of benzophenone favors 1e⁻ transfer for C–C bond formation.

Long Luo opened a general discussion of the paper by Seyyedamirhossein Hosseini: Reductive oxidation and oxidative reduction are very interesting reaction schemes. The different redox environments on the electrode surface *versus* in the solution near the electrode surface, can be utilized to achieve chemical transformations that cannot be accomplished otherwise. What are the unique reactions you think can be potentially achieved using your reductive oxidation or oxidative reduction (<https://doi.org/10.1039/d3fd00067b>)?

Seyyedamirhossein Hosseini and Joshua A. Beeler responded: Opportunities in this system lie in the follow-up reactions that would be impossible to achieve using direct electrolysis. For example, the halogenation of toluene would not be possible using direct toluene oxidation since halogen oxidation to the halide would occur simultaneously. However, reductive oxidation can be used to oxidize toluene at an applied potential of –0.2 V, meaning that direct halogen oxidation can be avoided.

Long Luo queried: Sulfate radicals can be conveniently generated by mild heating, UV irradiation, or sonication of a Na₂S₂O₈ solution. What are the advantages of using electrochemistry?

Richard C. D. Brown commented: I really like the concept described in the paper, where strong oxidants (or reductants) are generated by electrochemical reduction (or oxidation) under relatively mild conditions using mediators. This could be a very powerful and useful approach in electrosynthesis.

As a comment in response to Long Luo's question on the difference between the electrochemical approach to generating sulfate radical anions from peroxydisulfate and the thermal alternative (heating peroxydisulfate): assuming even temperature distribution in the thermal reaction, the sulfate radical anion will be generated throughout the solution, wherever peroxydisulfate is present. On the other hand, the electrochemical method will give different concentration profiles of sulfate radical anions depending on the flux of the mediator (reduction) from the electrode and the relative rates of the follow-up electron-transfer and chemical steps. Thus, some additional opportunities for control may be possible in the electrochemical method described in your presented paper.

Joshua A. Beeler responded: This comment from Richard C. D. Brown answers Long Luo's question. The non-electrochemical methods used previously generate an even distribution of sulfate radical anions throughout the solution. However, using the electrochemical method, sulfate radical anion is generated at a high concentration away from the electrode surface via the reaction with the mediator. This allows one to control the reaction kinetics and provides opportunities for follow-up chemical steps.

Naoki Shida asked: For the reductive oxidation system, is the reactivity of active species closer to a single-electron oxidant via outer-sphere electron transfer? Or does it show the hydrogen atom abstraction type of reactivity?

Joshua A. Beeler answered: The reductive oxidation system shows hydrogen atom abstraction reactivity. A detailed explanation can be found in our previous publication.¹

¹ S. Hosseini, J. N. Janusz, M. Tanwar, A. D. Pendergast, M. Neurock and H. S. White, *J. Am. Chem. Soc.*, 2022, 144, 21103–21115.

Naoki Shida addressed Joshua A. Beeler and Seyyedamirhossein Hosseini: In the manuscript, you demonstrate the oxidation of tertiary C–H bonds by avoiding the oxidation of primary amines. Primary amines are generally easily oxidized, but this reductive oxidation system avoids such reaction by generating reactive species under very mild anodic potential. Is there any oxidatively weak functional group that is compatible with this reaction, such as carboxylic acid (which easily undergoes Kolbe-type reaction) and olefins?

Joshua A. Beeler responded: We protected the amine groups via protonation. We were able to carry out C–H activation in the presence of a number of functional groups such as halides, sulfonyl, carboxyl, and amine groups using reductive oxidation.

Richard C. D. Brown asked: For the mediated electrosyntheses described in your work, did you investigate different mediators that are more difficult to reduce or oxidize relative to the substrate in the preparative experiments? For example, did you try to perform the mediated oxidation of oxalate in the presence of a mediator possessing a more positive oxidation potential?

Joshua A. Beeler answered: All mediators that were screened for persulfate reduction and oxalate oxidation are discussed in our paper. For the reductive oxidation system (i.e., mediated persulfate reduction), we screened four different mediators, see Fig. 2 in our paper. For the oxidative reduction system (i.e., mediated oxalate oxidation), three mediators were screened, as shown in Fig. 6 in our paper.

Richard C. D. Brown addressed Seyyedamirhossein Hosseini and Joshua A. Beeler: Following on from my previous question, I emphasise that the question related to the preparative experiment rather than the cyclic voltammetry.

Joshua A. Beeler replied: We did not try other mediators in the preparative experiment.

Robert Francke addressed Joshua A. Beeler and Seyyedamirhossein Hosseini: In your work, one electron reduction/oxidation of radical intermediates derived from peroxydisulfate and oxalate, respectively, are described as unproductive pathways. The radicals seem to be rapidly converted at the electrode surface, but react slowly with the activated form of the mediator. Do you have an explanation for the difference between the rates of these competing processes?

Joshua A. Beeler responded: The reaction rate for the $1e^-$ quenching of SO_4^- and CO_2^- by the active form of the electrocatalyst is very rapid and occurs at approximately the same rate for both species.

Robert Francke addressed Joshua A. Beeler and Seyyedamirhossein Hosseini: Since the generation of radical intermediates has to proceed with a certain spatial distance to the electrode, one seems to face a dilemma: on the one hand, mediators have to be employed, which react relatively slowly (otherwise, radical formation occurs close to the electrode); on the other hand, high overall reaction rates are desired. Is there a way to address this issue or do you think that this compromise is acceptable?

Joshua A. Beeler answered: Indeed, we would like to employ an electrocatalyst that exhibits a large rate constant for the homogeneous reduction of peroxydisulfate. As facile electrocatalysis enables the generation of a higher concentration of SO_4^- , which in return increases the efficiency of the oxidation reaction.

Robert Francke addressed Joshua A. Beeler and Seyyedamirhossein Hosseini: How many equivalents peroxydisulfate/oxalate were typically employed? How much was consumed during electrolysis?

Joshua A. Beeler responded: The optimal value of peroxydisulfate equivalents depends on the oxidation reaction. For example, 10 and 20 equivalents were used for alcohol oxidation to the aldehyde and carboxylic acid, respectively. For specifics concerning reaction yield vs. equivalents of persulfate, see Table S2–S4 in ref. 1. All persulfate initially present is consumed by the end of the electrolysis.

1 A. Hosseini, J. N. Janusz, M. Tanwar, A. D. Pendergast, M. Neurock and H. S. White, *J. Am. Chem. Soc.*, 2022, 144, 21103–21115.

Belen Batanero addressed Seyyedamirhossein Hosseini and Joshua A. Beeler: How difficult is it to solve organic compounds under your experimental aqueous conditions; a process subjected to oxidative reactions, water, which limit organic synthesis. Have you tried to apply it to some specific organic compound? How were the results?

Joshua A. Beeler answered: As outlined in our paper, various organic compounds are dissolved through the addition of 10 to 20% acetonitrile by volume, to the aqueous solutions. For examples of specific organic compounds, see Fig. 4 in our paper.

Conflicts of interest

There are no conflicts to declare.