Electrochemical Asymmetric Diacetoxylation of Styrenes Mediated by Chiral Iodoarene Catalyst

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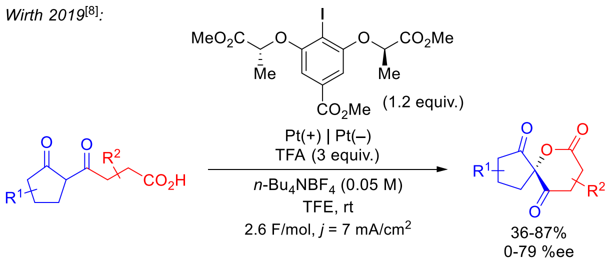
Abstract

Organocatalysis with chiral iodoarenes has emerged as a powerful approach for performing enantioselective transformations, however, suffering from the need to utilize stoichiometric amounts of peroxy acids or similar high energy oxidants. Electrosynthesis enables eliminating stoichiometric redox reagents by replacing them with electric stimuli. In this context, an electrochemically-promoted variant of the chiral iodoarene-catalyzed asymmetric diacetoxylation of styrenes was evaluated. The screening of reaction parameters established a set of conditions under which, for the first time, an enantioselective electrochemical oxidation mediated by a chiral iodoarene achieving a catalytic turnover has been accomplished. The reaction was applied for the synthesis of an array of products in 15-60% yields and 0-84% ee. The modest efficiency of the electrocatalysis was traced to a partial direct oxidation of styrene substrates leading to racemic products and undesired dimeric side-products. Cyclic voltammetry measurements demonstrated that such outcome originates from a somewhat difficult electrochemical oxidation of the applied iodoarene catalyst. Present work provides

important insights and implications for the design of more efficient electrocatalytic systems employing chiral iodoarenes as mediators.

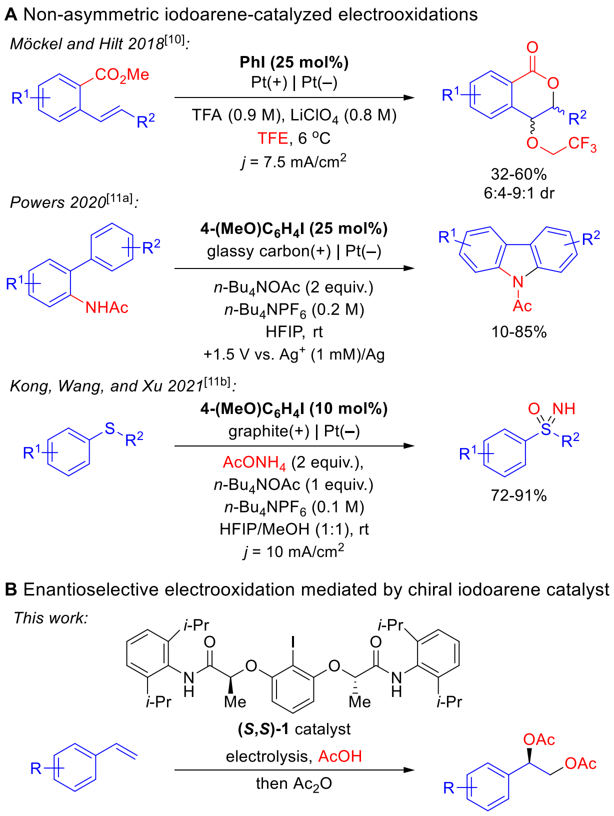
Introduction

Hypervalent iodine compounds have been extensively applied in oxidative transformations, often involving the formation of new C–C and C–heteroatom bonds, and resulting in a large increase of the molecular complexity.[1] An important breakthrough in the area of oxidations with the hypervalent iodine species came with the discovery that this type of reactions may be carried out using a catalytic amount of iodine-containing reagent by an *in situ* reoxidation of iodoarene back into the active hypervalent form using a suitable terminal oxidant.[2] Probably the most significant benefit of this advancement was creating the opportunity for the development of practical asymmetric variants of the reactions leading to chiral products, as only small affordable amounts of the precious chiral reagents were now required. Over the last 15 years a number of such enantioselective catalytic reactions employing chiral iodine-containing compounds have been reported.[3] Although, the iodoarene organocatalysis has gained momentum, it still requires the use of a stoichiometric oxidant, which remains its inherent drawback. *meta*-Chloroperbenzoic acid (*m*CPBA) and other peroxy acids have been most commonly applied in this role and as much as 3 equivalents of the oxidant are often required in practical protocols.



Scheme 1. The only existing electrochemical enantioselective oxidation employing chiral iodoarene as a mediator, used in a stoichiometric amount.

Electrosynthesis is an attractive approach to sustainable chemistry allowing to efficiently provide the driving force for redox transformations, eliminating the need for high energy stoichiometric oxidants and reductants, and the generation of attendant waste streams.[4] Thus, the electrochemical approach addresses the major downside associated with the oxidative transformations involving hypervalent iodine species. Indeed, already in the 20th century the electrochemical generation of I(III) reagents and their application in oxidative processes has been reported.[5] Up to now, many other examples of indirect electrolysis employing iodoarenes as redox mediators have been developed.[6-7] These reactions, however, engage a stoichiometric amount of the hypervalent iodine reagent either in an ex-cell fashion, that is, wherein iodoarene is first electrolyzed in the absence of organic substrate, or in-cell, i.e., with the mediator and substrate both present during the electrolysis. Among them, there is the single existing example of using a stoichiometric chiral iodoarene to effect the enantioselective oxidative lactonization of 1,3-diketones under electrochemical conditions, reported by Witrh in 2019 (Scheme 1).[8]



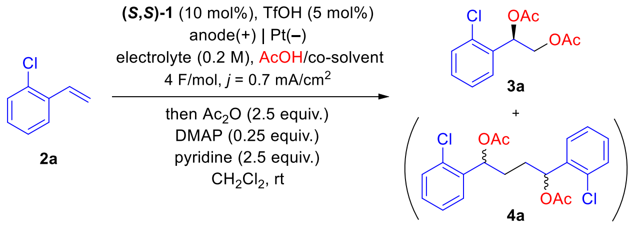
Scheme 2. (A) Selected examples of non-asymmetric electrochemical oxidations mediated by iodoarene catalysts and (B) the enantioselective reaction employing a chiral iodoarene as an electrocatalyst, reported herein. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol, TFE = 2,2,2-trifluoroethanol.

The true indirect electrocatalysis[9] with iodoarenes, in which small amounts of these compounds convey applied potential from the anode to a substrate with multiple turnovers, has been achieved for the first time in 2018 by Möckel and Hilt (Scheme 2A).[10] This concept, being the rightful electrochemical equivalent to the iodoarene organocatalysis employing chemical oxidants, has been since pursued in several works by other groups (Scheme 2A).[11] Nevertheless, to the best of our knowledge, no asymmetric electrosynthetic reaction[12] employing a chiral iodoarene catalyst has been yet accomplished to date. In this context, herein we establish that such transformation can indeed be achieved. In particular, we report an enantioselective electrochemical diacetoxylation of styrenes mediated by a chiral Ishihara-Muñiz C_2-symmetric iodoresorcinol-lactamide catalyst **(*S*,*S*)-1** (Scheme 2B).[13]

Result and discussion

The enantioselective diacetoxylation of styrenes promoted by chiral hypervalent iodine species has been first reported by Fujita using a stoichiometric quantity of I(III) reagent.[14] This was followed by the development of the catalytic version by Ishihara and Muñiz, employing catalyst **1** in a combination with peracetic acid as the terminal oxidant.[13] As no better system has been since reported,[15] we adopted chiral iodoarene **(*S*,*S*)-1** for the electrochemical reaction.

Table 1. Optimization of reaction conditions.



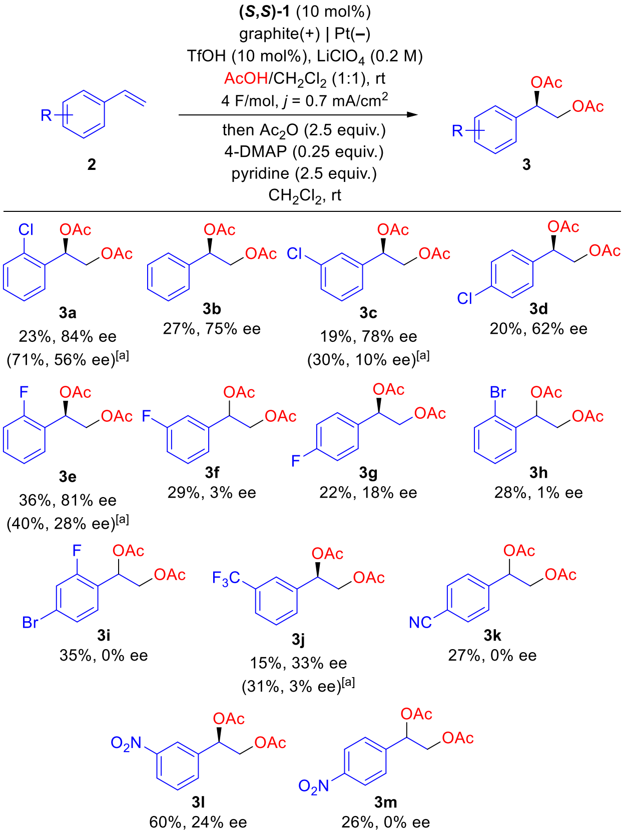
Entry	Conditions	Yield (%)[a]	ee (%)[b]
1	Graphite(+), AcOH, *n*-Bu_4NPF_6	22	56
2	Graphite(+), AcOH/HFIP (1:1), *n*-Bu_4NPF_6	2	Nd
3	Graphite(+), AcOH/MeCN (1:1), *n*-Bu_4NPF_6	4	Nd
4	Graphite(+), AcOH/$MeNO_2$ (1:1), *n*-Bu_4NPF_6	12	58
5	Graphite(+), AcOH/DMF (1:1), *n*-Bu_4NPF_6	7	Nd
6	Graphite(+), AcOH/CH_2Cl_2 (1:1), *n*-Bu_4NPF_6	22	60
7	Graphite(+), AcOH/CH_2Cl_2 (1:1), *n*-Bu_4NBF_4	10	50
8	Graphite(+), AcOH/CH_2Cl_2 (1:1), $NaBF_4$	3	Nd
9	Graphite(+), AcOH/CH_2Cl_2 (1:1), Et_4NOTs	20	48
10	Graphite(+), AcOH/CH_2Cl_2 (1:1), $KBrO_3$	10	47
11	Graphite(+), AcOH/CH_2Cl_2 (1:1), $NaClO_4$	27	66
12	Graphite(+), AcOH/CH_2Cl_2 (1:1), $LiClO_4$ (***best ee***)	29	84
13	Glassy carbon(+), AcOH/CH_2Cl_2 (1:1), $LiClO_4$ (***best yield***)	48	58
14	Graphite(+), AcOH/CH_2Cl_2 (1:1), $LiClO_4$, no catalyst	18	Nd
15	Glassy carbon(+), AcOH/CH_2Cl_2 (1:1), $LiClO_4$, no catalyst	32	Nd

[a] Determined by ^1H NMR spectroscopy. [b] Determined by HPLC on a chiral stationary phase. DMAP = 4-dimethylaminopyridine, HFIP = 1,1,1,3,3,3-hexafluoroisopropanol, Nd = not determined.etermined by ^1H NMR spectroscopy.

Employing 2-chlorostyrene **2a** as the model substrate, we started the optimization of the reaction parameters from the conditions consisting of 10 mol% of **(*S*,*S*)-1**, 5 mol% of TfOH to activate the corresponding I(III) diacetate,[16] and acetic acid as the solvent. The electrolysis was carried out in a constant current mode in an undivided cell, using graphite anode and platinum cathode, and *n*-Bu_4NPF_6 as the supporting electrolyte (Table 1, entry 1). Under these conditions, similarly as in the case of the reaction employing chemical oxidant,[13] a mixture of the desired diacetoxy styrene with two regioisomeric acetoxy alcohols is formed, thus, a subsequent acetylation was performed to convert all the material into **3a**. The reaction afforded the product in 22% yield and 56% ee, proving the involvement of chiral catalyst. The low yield in this and the subsequent reactions using graphite anode could be traced to the partial dimerization of the substrate, furnishing side-product **4a**, which is a viable pathway during the direct anodic oxidation of styrenes.[17]

Next, we tested different co-solvents (Table 1, entries 2-6). Interestingly, those commonly applied in electrosynthesis, such as HFIP, MeCN, $MeNO_2$, and DMF were all found to be detrimental for the reaction, while the use of CH_2Cl_2 resulted in the same yield, but a slightly increased ee relative to pure acetic acid (entry 6 vs. 1). The screening of supporting electrolytes in $AcOH/CH_2Cl_2$ solvent system (entries 7-12) identified $LiClO_4$ as the optimal one, maximizing the enantioselectivity (entry 12). The product ee of 84% obtained under these conditions almost matches the one in the reaction using chemical oxidant (90% ee[13]). Therefore, a catalytic turnover has been clearly achieved, although with a rather low turnover number of slightly below 3. As mentioned above, the limited yield is due to the formation of **4a** via a direct oxidation of substrate on the graphite anode. Since the oxidation potential of styrene has been reported to be higher on glassy carbon,[17] we tested also this electrode material. Indeed, the yield of desired product increased to 48%, however, at the expense of the enantioselectivity (entry 13). Additional screening of the reaction parameters, including other anode and cathode materials, current densities, temperatures, etc., did not result in further improvement of the results (see Tables S1 and S2 in the Supporting information).

Finally, we carried out control experiments without the catalyst, which demonstrated that product **3a** can form to some extent via a direct electrolysis (entries 14 and 15). However, for graphite anode, the high ee testifies that the great majority of the product has to be generated with the intermediacy of **(*S*,*S*)-1**, when the catalyst is present (entry 12). Conversely, in the case of glassy carbon anode, a considerable amount of **3a** (approx. one third) may originate from the direct electrolysis of the substrate (entry 13).



Scheme 3. Scope of the diacetoxylation of styrenes mediated by chiral iodoarene catalyst **(*S*,*S*)-1** (isolated yields). [a] Using a glassy carbon anode.

The established reaction conditions were then applied to an array of substituted styrenes to explore the scope of the enantioselective electrochemical diacetoxylation using the chiral iodoarene catalyst (Scheme 3). For each substrate, the electrolysis was performed with both graphite and glassy carbon anodes, however, the latter was not found to be universally better in the terms of the product yield. Thus, the results for the glassy carbon anode are reported in

Scheme 3 only if they surpass the ones for graphite (see Scheme S1 for all the results). To this end, product **3a** was isolated in the preparative scale in 23% yield in 84% ee using graphite anode. In turn, the application of glassy carbon anode affords **3a** in 71% yield and 56% ee. Qualitatively similar outcomes, i.e., 20-40% yield and 60-80% ee, were obtained for the unsubstituted styrene (**3b**), 3- and 4-chlorostyrenes (**3c-d**), and 2-fluorostyrene (**3e**). In the case of other tested compounds, the products were also afforded with analogous efficiencies, except for 3-nitro-substituted one that was furnished in a better 60% yield (**3l**). However, the attained enantioselectivities decreased to 20-30% ee for some of the products (**3g**, **3j**, **3l**) and were virtually nonexistent for the other (**3f**, **3h-i**, **3k**, **3m**). Since all these compounds have been previously synthesized in >80% ee using the same catalyst in the presence of chemical oxidant,[13] obtained results suggest that the direct electrolysis prevails in these instances (and mostly leads to the corresponding dimers of type **4**).

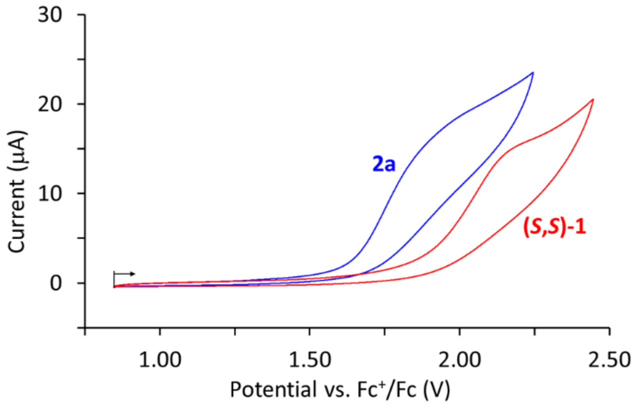


Figure 1. Cyclic voltammograms of iodoarene catalyst **(*S*,*S*)-1** (red) and 2-chlorostyrene **2a** (blue) in HFIP using a glassy carbon working electrode. [Analyte] = 2 mM, [*n*-Bu_4NPF_6] = 0.10 M, scan rate = 0.1 V·s^{-1}, counter electrode: Pt wire, reference electrode Ag/$AgPF_6$ (10 mM).

To gain some insight into the origin of the observed results, cyclic voltammetry measurements were carried out. The registered voltammograms for catalyst **(*S*,*S*)-1** and substrate **2a** using a glassy carbon electrode in HFIP (Figure 1) demonstrate that the onset oxidation potential of the former is clearly higher than the one of the latter (by ~0.2 V). Thus, the direct oxidation of the substrate without the involvement of the catalyst, both leading to racemic product **3** as well as to dimeric side-product **4**, is indeed hard to avoid. In fact, the recorded irreversible oxidation wave of **(*S*,*S*)-1** at $E_{p/2}$ ~2.0 V vs. Fc^+/Fc places this iodoarene catalyst at the high end of the scale regarding the difficulty of electrochemical oxidation.[18] This suggests that the popular Ishihara-Muñiz iodoresorcinol-lactamide chiral scaffold may not be the optimal choice for electrochemically-promoted reactions.

Conclusions

In summary, we have for the first time accomplished an enantioselective electrochemical oxidation mediated by a chiral iodoarene achieving a catalytic turnover. Although the efficiency of reaction is far from satisfactory, it constitutes a proof of concept that such transformations are possible. The inability of the applied iodoarene catalyst to undergo a facile electrochemical oxidation has been identified to be the key obstacle. Current results provide bearing for the design of novel asymmetric iodoarene-catalyzed electrosynthetic processes and may be an important stimulus for further developments in this area.

Experimental section

General Procedure for the electrochemical diacetoxylation of styrenes mediated by iodoarene catalyst (*S*,*S*)-1. A 10-mL glass vial was charged with catalyst **(*S*,*S*)-1**[19] (21.4 mg, 0.03 mmol, 10 mol%) and $LiClO_4$ (160 mg, 1.50 mmol). AcOH (3.75 mL) and CH_2Cl_2 (3.75 mL) were added to the vial, followed by substrate **2** (0.30 mmol) and TfOH (1.3 μL, 2.3

mg, 0.015 mmol, 5 mol%). The vial was closed with a cap fitted with a graphite anode and a platinum (coated on copper) cathode. The electrolysis was carried out at a constant current of 3.7 mA, with stirring at rt, until 4.0 F/mol was passed. The reaction mixture was diluted with CH_2Cl_2 and washed with brine. The aqueous phase was extracted once with CH_2Cl_2 and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (0.5 mL) and Ac_2O (72 μL, 78 mg, 0.75 mmol, 2.5 equiv.), pyridine (61 μL, 60 mg, 0.75 mmol, 2.5 equiv.), and DMAP (9.2 mg, 0.075 mmol, 0.25 equiv.) were added. After stirring overnight at rt, 3 M aqueous HCl was added (1 mL). The organic laver was separated and the aqueous phase was extracted once with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography.

Supporting Information

The Supporting Information file contains: results of additional optimization experiments; isolated yields using glassy carbon anode; characterization data, HPLC chromatograms, and NMR spectra for products.

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Notes

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References

[1] a) Y. Kita, T. Dohi, *Chem. Rec.* **2015**, *15*, 886-906; b) R. Narayan, S. Manna, A. P. Antonchick, *Synlett* **2015**, *26*, 1785-1803; c) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328-3435; d) *Top. Curr. Chem., Vol. 373* (Ed. T. Wirth), Springer, Switzerland, **2016**; e) A. J.-D. Lauriers, C. Y. Legault, *Asian J. Org. Chem.* **2016**, *5*, 1078-1099; f) Y. Yoshimura, H. Wakamatsu, Y. Natori, Y. Saito, N. Minakawa, *Beilstein J. Org. Chem.* **2018**, *14*, 1595-1618; g) F. V. Singh, P. B. Kole, S. R. Mangaonkar, S. E. Shetgaonkar, *Beilstein J. Org. Chem.* **2018**, *14*, 1778-1805; h) I. F. D. Hyatt, L. Dave, N. David, K. Kaur, M. Medard, C. Mowdawalla, *Org. Biomol. Chem.* **2019**, *17*, 7822-7848; i) A. Bauer, N. Maulide, *Chem. Sci.* **2021**, *12*, 853-864.

[2] a) T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma, Y. Kita, *Angew. Chem. Int. Ed.* **2005**, *44*, 6193-6196; b) R. D. Richardson, T. Wirth, *Angew. Chem. Int.*

Ed. **2006**, *45*, 4402-4404; c) T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073-2085; d) M. S. Yusubov, V. V. Zhdankin, *Resour. Effic. Tech.* **2015**, *1*, 49-67.

[3] a) M. Ngatimin, D. W. Lupton, *Aust. J. Chem.* **2010**, *63*, 653-658; b) F. V. Singh, T. Wirth, *Chem. Asian J.* **2014**, *9*, 950-971; c) R. M. Romero, T. H. Wöste, K. Muñiz, *Chem. Asian J.* **2014**, *9*, 972-983; d) F. Berthiol, *Synthesis* **2015**, *47*, 587-603; e) S. Ghosh, S. Pradhan, I. Chatterjee, *Beilstein J. Org. Chem.* **2018**, *14*, 1244-1262; f) A. Claraz, G. Masson, *Org. Biomol. Chem.* **2018**, *16*, 5386-5402; g) X. Li, P. Chen, G. Liu, *Beilstein J. Org. Chem.* **2018**, *14*, 1813-1825; h) A. Flores, E. Cots, J. Bergès, K. Muñiz, *Adv. Synth. Catal.* **2019**, *361*, 2-25; i) F. V. Singh, S. E. Shetgaonkar, M. Krishnan, T. Wirth, *Chem. Soc. Rev.* **2022**, *51*, 8102-8139.

[4] a) E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *2*, 302-308; b) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230-13319; c) J.-i. Yoshida, A. Shimizu, R. Hayashi, *Chem. Rev.* **2018**, *118*, 4702-4730; d) Y. Jiang, K. Xu, C. Zeng, *Chem. Rev.* **2018**, *118*, 4485-4540; e) M. D. Kärkäs, *Chem. Soc. Rev.* **2018**, *47*, 5786-5865; f) A. Shatskiy, H. Lundberg, M. D. Kärkäs, *ChemElectroChem* **2019**, *6*, 4067-4092; g) T. H. Meyer, I. Choi, C. Tian, L. Ackermann, *Chem* **2020**, *6*, 2484-2496; h) D. Pollok, S. R. Waldvogel, *Chem. Sci.* **2020**, *11*, 12386-12400; i) C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu, L. Ackermann, *ACS Cent. Sci.* **2021**, *7*, 415-431.

[5] Selected seminal reports: a) T. Fuchigami, T. Fujita, *J. Org. Chem.* **1994**, *59*, 7190-7192; b) T. Fujita, T. Fuchigami, *Tetrahedron Lett.* **1996**, *37*, 4725-4728; c) S. Hara, T. Hatakeyama, S.-Q. Chen, K. Ishi-i, M. Yoshida, M. Sawaguchi, T. Fukuhara, N. Yoneda, *J. Fluor. Chem.* **1998**, *87*, 189-192.

[6] Review: M. Elsherbini, T. Wirth, *Chem. Eur. J.* **2018**, *24*, 13399-13407.

[7] Selected examples: a) T. Sawamura, S. Kuribayashi, S. Inagi, T. Fuchigami, *Adv. Synth. Catal.* **2010**, *352*, 2757-2760; b) T. Sawamura, S. Kuribayashi, S. Inagi, T. Fuchigami, *Org. Lett.* **2010**, *12*, 644-646; c) D. Kajiyama, T. Saitoh, S. Nishiyama, *Electrochemistry* **2013**, *81*, 319-324; d) T. Broese, R. Francke, *Org. Lett.* **2016**, *18*, 5896-5899; e) O. Koleda, T. Broese, J. Noetzel, M. Roemelt, E. Suna, R. Francke, *J. Org. Chem.* **2017**, *82*, 11669-11681; f) A. F. Roesel, T. Broese, M. Májek, R. Francke, *ChemElectroChem* **2019**, *6*, 4229-4237; g) M. Elsherbini, B. Winterson, H. Alharbi, A. A. Folgueiras-Amador, C. Génot, T. Wirth, *Angew. Chem. Int. Ed.* **2019**, *58*, 9811-9815; h) S. Doobary, A. T. Sedikides, H. P. Caldora, D. L. Poole, A. J. J. Lennox, *Angew. Chem. Int. Ed.* **2020**, *59*, 1155-1160.

[8] W.-C. Gao, Z.-Y. Xiong, S. Pirhaghani, T. Wirth, *Synthesis* **2019**, *51*, 276-284.

[9] a) R. Francke, R. D. Little, *Chem. Soc. Rev.* **2014**, *43*, 2492-2521; b) J. C. Siu, N. Fu, S. Lin, *Acc. Chem. Res.* **2020**, *53*, 547-560; c) R. Francke, *CHIMIA* **2020**, *74*, 49-56.

[10] R. Möckel, E. Babaoglu, G. Hilt, *Chem. Eur. J.* **2018**, *24*, 15781-15785.

[11] a) A. Maity, B. L. Frey, N. D. Hoskinson, D. C. Powers, *J. Am. Chem. Soc.* **2020**, *142*, 4990-4995; b) X. Kong, L. Lin, X. Chen, Y. Chen, W. Wang, B. Xu, *ChemSusChem* **2021**, *14*, 3277-3282; c) S. A. Paveliev, O. O. Segida, O. V. Bityukov, H.-T. Tang, Y.-M. Pan, G. I. Nikishin, A. O. Terent'ev, *Adv. Synth. Catal.* **2022**, *364*, 3910-3916; d) B. L. Frey, M. T. Figgins, G. P. Van Trieste, III, R. Carmieli, D. C. Powers, *J. Am. Chem. Soc.* **2022**, *144*, 13913-13919; e) M. Elsherbini, W. J. Moran, *J. Org. Chem.* **2023**, *88*, 1424-1433.

[12] C. Margarita, H. Lundberg, *Catalysts* **2020**, *10*, 982.

[13] S. Haubenreisser, T. H. Wöste, C. Martínez, K. Ishihara, K. Muñiz, *Angew. Chem. Int. Ed.* **2016**, *55*, 413-417.

[14] M. Fujita, M. Wakita, T. Sugimura, *Chem. Commun.* **2011**, *47*, 3983-3985.

[15] T. H. Wöste, K. Muñiz, *Synthesis* **2016**, *48*, 816-827.

[16] Y.-B. Kang, L. H. Gade, *J. Am. Chem. Soc.* **2011**, *133*, 3658-3667.

[17] R. Engels, H. J. Schäfer, E. Steckhan, *Justus Liebigs Ann. Chem.* **1977**, *1977*, 204-224.

[18] B. L. Frey, P. Thai, L. Patel, D. C. Powers, *Synthesis* **2023**, 10.1055/a-2029-0617.

[19] E. Cots, J. Rintjema, F. Bravo, K. Muñiz, *Org. Lett.* **2021**, *23*, 6429-6434.