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Intramolecular Electrochemical Oxybromination of Olefins for the Synthesis of Isoxazolines in Batch and Continuous Flow

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A highly regioselective protocol for the synthesis of isoxazolines through cascade C–O and C–Br bond formation has been developed. The electrochemical approach uses traceless electrons as a sole source of oxidant, thus avoiding the use of stoichiometric organic or inorganic oxidants and provides a mild and environmentally benign alternative pathway for the synthesis of a wide range of valuable substituted isoxazolines from alkenyl oximes in good yields.

Synthetic organic chemistry is considered a fast-developing field in science as it continuously provides new routes towards the synthesis of novel materials via green, sustainable, and economical techniques.[1,2] Electrochemical synthetic methods have gained increasing attention since they provide mild conditions, good functional group tolerance, high regioselectivity and chemoselectivity, and reduced waste by avoiding costly oxidants or reductants in favor of electricity.[3]

Nitrogen-containing heterocycles are important building blocks and part of many commercial products. Among them, isoxazolines are an important class of heterocyclic compounds and their derivatives are frequently found in a wide range of natural products, biologically active compounds, agrochemicals, and pharmaceuticals.[4,5] (Figure 1) Moreover, isoxazolines can serve as versatile synthetic intermediates in organic chemistry.[6–11] Therefore, the development of sustainable methods providing isoxazolines and their derivatives remains an important target for synthetic organic chemists. Approaches for their synthesis range from the use of the 1,3-dipolar cycloaddition reactions of nitrile oxides with allyl halide[12,13] to oxyhalogenation of allylic oximes.[14,15]

In many instances, these methods not only require the use of transition metal catalysts, high temperature or toxic, costly, organic or inorganic oxidizing agents but also suffer from low to moderate yields. However, progress in the oxyhalogenation reaction has been made recently and examples include Pd,[15a] Fe[15b] Cu,[15c] or Al[15d] or TBHP[15e] mediated protocols. Furthermore, molecular bromine was applied in the cyclization, albeit with varying yields and the observation of side reactions.[15f] Hence, the development of a simple, economically viable, and

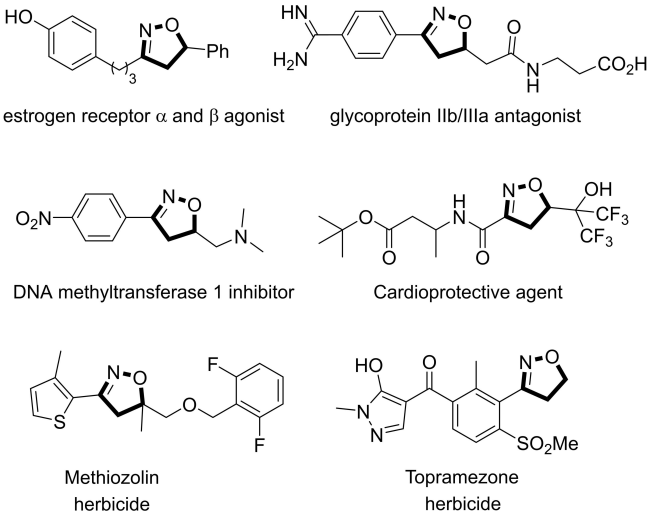

Figure 1. Examples of 2-isoxazoline containing biologically-active molecules.

complementary environmentally friendly way to access isoxazolines is desirable. Based on our interest in synthetic electrochemistry,[16] we decided to explore the electrochemical oxyhalogenation for the synthesis of bromomethyl substituted isoxazolines starting from allylic oximes, although being aware that the base mediated electrochemical oxime cyclization via the formation of oxime radicals[17] leads to the unwanted isoxazoles.[18] However, by choice of an electrolyte that also acts as the halogen source, the desired bromomethyl substituted isoxazolines could be accessible.

Readily available β,γ-unsaturated ketoxime **1a** was therefore chosen as our model substrate and potassium bromide as both electrolyte and source of bromine to reduce waste production. We decided to use an undivided cell with a graphite anode and a stainless-steel cathode. Initially, different reaction parameters were evaluated (Table 1). The use of solvents such as MeOH, gave a trace amount of product (Table 1, entry 1), and THF, or dioxane yielded no detectable product (Table 1, entry 2). A mixture of MeCN:H_2O (3:1) provided two cyclization products **2a** and **3a** in a 3:2 ratio (Table 1, entry 3).

Changing the solvent to DMSO:H_2O increased the yield to 85% (Table 1, entry 4). Furthermore, increased current density resulted in better yield (Table 1, entry 5, 6). The best conditions proved to be 70 mA/cm^2 for 20 min and provided the product in 95% GC yield and 74% isolated yield. Further increasing current density to 100 mA/cm^2 did not give a better yield (Table 1, entry 7). Using neat DMSO or DMF resulted in lower

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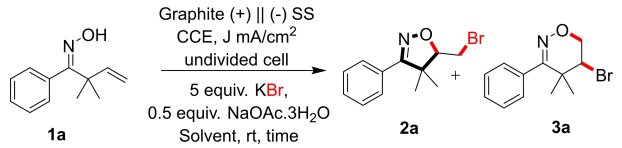
Table 1. Optimization of Reaction Conditions.[a]

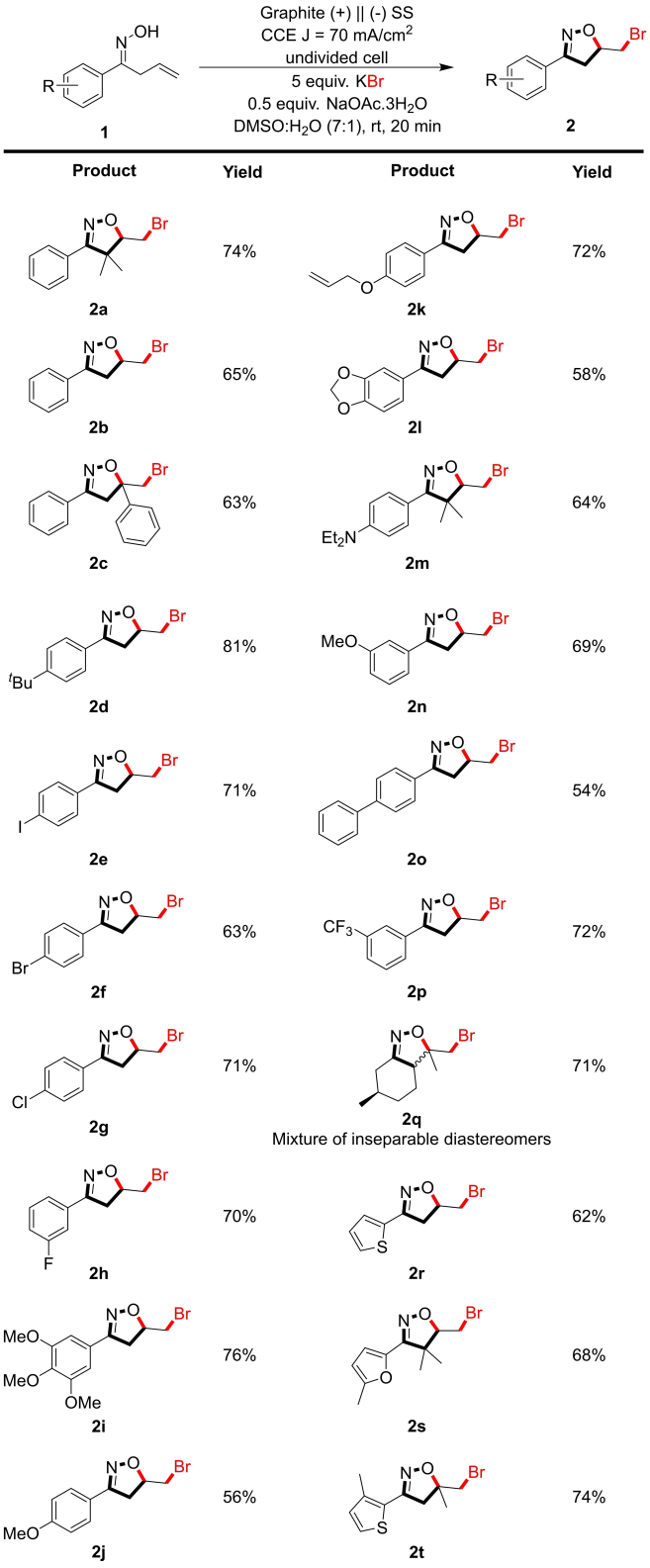


Entry	J [mA/cm^2]	Base	Solvent	Time	GC Yield [%]
1	10	–	MeOH	4 h	trace
2	10	–	THF:Dioxane	4 h	nr
3	10	NaOAc·3H$_2$O	MeCN:H$_2$O	4 h	51 **2a:3a**
4	10	NaOAc·3H$_2$O	DMSO:H$_2$O	5 h	85
5	30	NaOAc·3H$_2$O	DMSO:H$_2$O	1 h	86
6	70	NaOAc·3H$_2$O	DMSO:H$_2$O	20 min	95
7	100	NaOAc·3H$_2$O	DMSO:H$_2$O	20 min	92
8	10	NaOAc·3H$_2$O	DMSO	4 h	52
9	10	NaOAc·3H$_2$O	DMF	4 h	44
10	10	–	DMSO:H$_2$O	4 h	40
11	–	NaOAc·3H$_2$O	DMSO:H$_2$O	4 h	nr
12[b]	70	NaOAc·3H$_2$O	DMSO:H$_2$O	20 min	86
13[c]	70	NaOAc·3H$_2$O	DMSO:H$_2$O	20 min	89

[a] Reaction conditions: graphite anode, stainless steel cathode, **1a** (1.0 equiv., 0.2 mmol, 0.05 M), KBr (5 equiv., 1.0 mmol), NaOAc·3H$_2$O (0.5 equiv., 0.1 mmol), DMSO:H$_2$O (7:1) 4 mL, rt = room temperature, CCE = Constant Current Electricity J (mA/cm^2), Yields were determined by CC using benzoxazole as an internal standard. All reactions are performed under air. [b] Graphite is used as cathode instead of Stainless Steel. [c] Reaction is performed under argon. nr = no reaction.

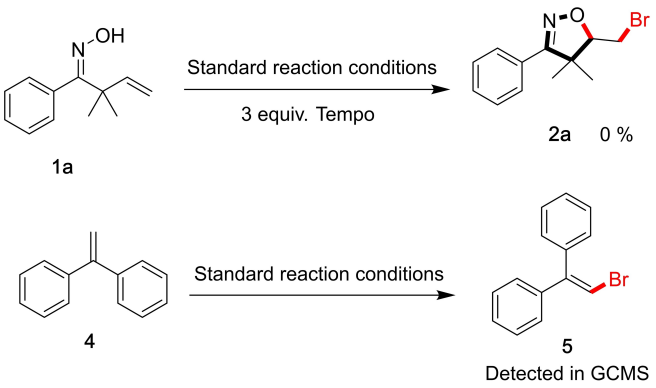
yields of the desired product (Table 1, entry 8,9). Addition of base NaOAc·3H$_2$O remained crucial, and without base, the reaction yield decreased to 40% (Table 1, entry 10). Electric current was also essential for the reaction to take place (Table 1, entry 11). Reaction worked fine under Argon atmosphere giving product in 86% yield. Other electrode materials such as silver, copper, glassy carbon, and RVC resulted in diminishing yields. During the reaction, we did not observe a significant increase in solution temperature. No noticeable degradation or fouling of electrodes was witnessed and the same electrodes were used after a simple cleaning procedure (See supporting information). We further explored the effect of concentration on the reaction mixture. To our delight, we achieved a good yield of desired product **2a** with a 5-fold increase of substrate concentration to 0.25 M. Similar yields were obtained when other electrolytes and bromine sources such as tetrabutylammonium bromide were used.

Given the good shelf life of potassium bromide, we decided to use it in all further experiments. However, other halide sources such as potassium iodide and tetrabutylammonium chloride can also be used and provide the iodo- and chloro-substituted 2-isoxazolines as products. With the optimized reaction conditions in hand, we started to explore the substrate scope by using a variety of substituted allylic oximes. The substrate scope was found to be rather general (Scheme 1). Different allylic ketoximes can be applied and provide the corresponding isoxazolines in good yields (**2a**-**d**). Substrates with more sensitive functional groups, such as allyloxy ether or methylenedioxy substitution were readily converted into the desired products (**2k**) and (**2l**), respectively. Halogen substitu-



Scheme 1. Substrate Scope of 2-Isoxazolines.- Reaction conditions: graphite anode, stainless steel cathode, 1a (1.0 equiv., 0.2 mmol, 0.05 M), KBr (5 equiv., 1.0 mmol), NaOAc·3H$_2$O (0.5 equiv., 0.1 mmol), DMSO:H$_2$O (7:1) 4 mL, current density = 70 mA/cm^2 (4.3 F/mol), rt = room temperature, time t = 20 min. All reactions are performed under air.

ents such as iodo (**2e**), bromo (**2f**), chloro (**2g**) and fluoro (**2h**) remained untouched, and desired products were isolated in good yields. Reactants with electron-donating groups such as methoxy (**2i**, **2j**, **2n**) and amines (**2m**) also reacted smoothly. Trifluoromethyl groups are of great interest in medicinal and agrochemical sciences. We are delighted to see that the CF_3 group was also tolerated during the reaction to produce 72% product (**2p**) yield. The reaction conditions were also suitable for substrates bearing heterocyclic aromatics such as furan (**2s**), and thiophene (**2r**, **2t**). The 2-bromo-substituted 2-isoxazolines are also useful precursors for nucleophilic substitution reactions to synthesize valuable products as previously demonstrated.[14] The commercially available IKA electrosynthesizer ES-2.0 was used to assess the reproducibility of the reaction. We are pleased to see that it gives similar yields.

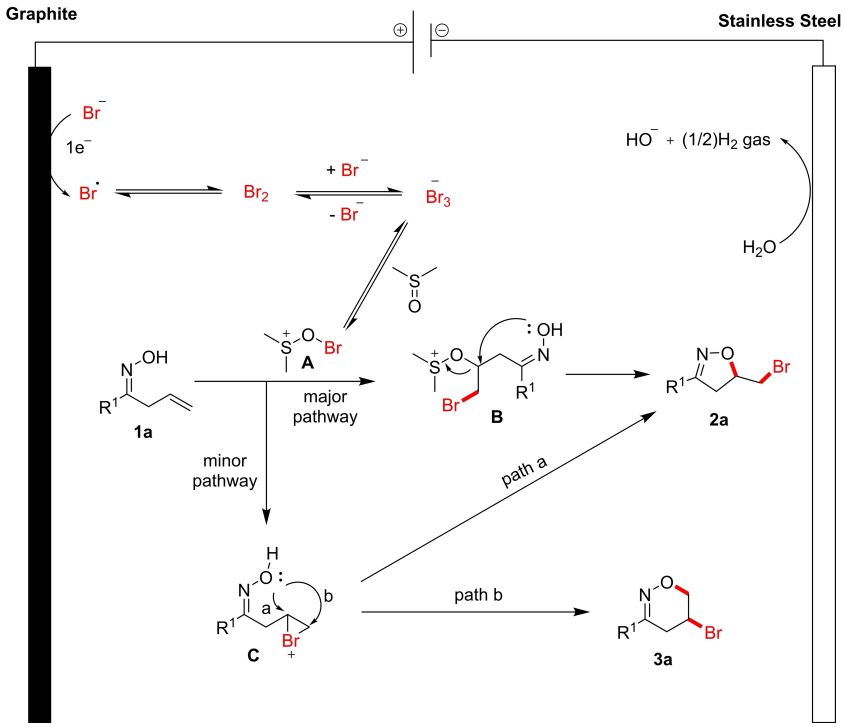


Scheme 2. Radical-trapping experiments.

To further gain information about reaction mechanism, we treated the allylic oxime **1a**, under the standard reaction conditions in the presence of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). However, no product was detected, implying that a radical process is involved in the catalytic cycle. We also performed another experiment with 1,1-diphenylethylene under standard reaction conditions and we successfully detected **5** in GCMS which supports the participation of bromine radical in the reaction mechanism (Scheme 2).

Based on our observations a plausible mechanism is proposed in Scheme 3. In the bromide-mediated electrochemical reaction, electro-oxidation of bromide (Br^-) at the anode leads to the formation of bromine, which is immediately captured by excess bromide (Br^-) to generate tribromide (Br_3^-) anion. The latter reacts with DMSO to form intermediate **A** (See supporting information Figure S6A and Figure S6B for more information).[19] Subsequently, **A** reacts with C=C double bonds to form **B** which further undergoes an intramolecular cyclization via nucleophilic attack of –OH of allyl ketoxime to form **2a**. Alternatively, **A** could react with **1a** to form a bromonium intermediate **C** which can react to **2a** via 5-exo-trig cyclization (path a). There is also the possibility of a 6-endo-trig cyclization which leads to by-product **3a** (path b). The evolution of molecular hydrogen (H_2) gas was observed at the cathode due to electrochemical water reduction. This reaction also generates an in-situ base needed for the oxime deprotonation.

Given the fast reaction time, we assumed that the oxybromination would be ideal for a continuous flow regime (Table 2). Reaction optimization was conducted in an Asia Syrris flow reactor (Scheme 4).

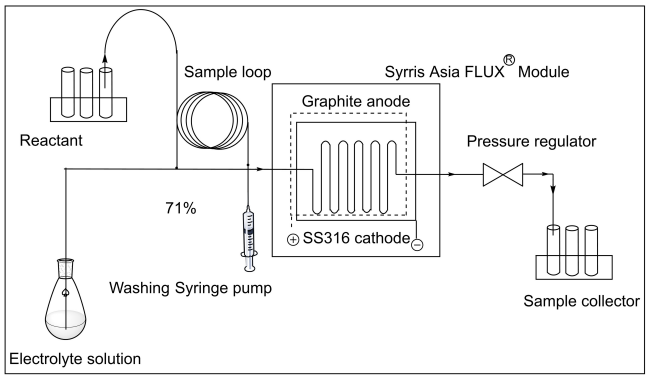


Scheme 3. Plausible Reaction Mechanism for Oxybromination of Allylic Oximes.

Table 2. Optimization of the Reaction Conditions using a Continuous Flow Reactor.[a]

Entry	J [mA/cm^2]	Flow rate [µl/min]	T [°C]	GC Yield [%]
1	100	100	rt	16
2	100	300	rt	70
3	100	400	rt	70
4	100	500	rt	71
5	100	600	rt	67
6	100	700	rt	68
7	100	800	rt	56
8	100	900	rt	69
9	100	200	40	56
10	100	300	40	55
11	100	200	20	86

[a] Reactions were conducted with 0.2 mmol **1a** in DMSO and KBr and NaOAc·3H_2O was dissolved in DMSO:H_2O, under constant current (CC) conditions. The electrochemical cell equipped with a graphite anode and an SS316 cathode and a Teflon separating gasket having an internal volume of 225 µl and 12 cm^2 of total surface area was used. Yields are determined by GC-FID.



Scheme 4. Electrochemical Continuous Flow Reactor.

Although the initial trials provided only little product, we were able to fine-tune the reaction parameters including flow rate and temperature to obtain the desired product in 86% yield (Table 2, entry 11). Thus, the newly developed reaction can be used both in batch and continuous flow processes which is crucial for further scale-up.

In summary, we have developed a new electrochemical method for the synthesis of 2-isoxazolines. The reaction operates under atmospheric conditions and tolerates air and moisture. Besides, the use of potassium bromide as both electrolyte and bromine source precludes the need for toxic, air-sensitive inorganic oxidants or transition metal catalysts. This method is, therefore, an attractive alternative for the synthesis of functionalized 2-isoxazolines.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Electrosynthesis · Flow electrosynthesis · 2-Isoxazolines · Oxybromination

[1] T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546–576.
[2] C. A. Kuttruff, M. D. Eastgate, P. S. Baran, *Nat. Prod. Rep.* **2014**, *31*, 419–432.
[3] a) O. R. Luca, J. L. Gustafson, S. M. Maddox, A. Q. Fenwick, D. C. Smith, *Org.Chem. Front.* **2015**, *2*, 823–848; b) *Organic Electrochemistry*, 5th ed (Eds.: O. Hammerich, B. Speiser), CRC, Boca Raton, **2015**.
[4] a) J. Wityak, T. M. Sielecki, D. J. Pinto, G. Emmett, J. Y. Sze, J. Liu, A. E. Tobin, S. Wang, B. Jiang, P. Ma, S. A. Mousa, R. R. Wexler, R. E. Olson, *J. Med. Chem.* **1997**, *40*, 50–60; b) J.-F. Cheng, Y. Huang, R. Penuliar, M. Nishimoto, L. Liu, T. Arrhenius, G. Yang, E. O'Leary, M. Barbosa, R. Barr, J. R. B. Dyck, G. D. Lopaschuk, A. M. Nadzan, *J. Med. Chem.* **2006**, *49*, 4055–4058; c) P. K. Poutiainen, T. A. Venäläinen, M. Peräkylä, J. M. Matilainen, S. Väisänen, P. Honkakoski, R. Laatikainen, J. T. Pulkkinen, *Bioorg. Med. Chem.* **2010**, *18*, 3437–3447; d) S. Castellano, D. Kuck, M. Viviano, J. Yoo, F. López-Vallejo, P. Conti, L. Tamborini, A. Pinto, J. L. Medina-Franco, G. Sbardella, *J. Med. Chem.* **2011**, *54*, 7663–7677.
[5] a) I. T. Hwang, H. R. Kim, D. J. Jeon, K. S. Hong, J. H. Song, K. Y. Cho, *J. Agric. Food Chem.* **2005**, *53*, 8639–8643; b) K. Grossmann, T. Ehrhardt, *Pest Manage. Sci.* **2007**, *63*, 429–439; c) K.-H. Hwang, J.-S. Lim, S.-H. Kim, M.-S. Jeon, D.-G. Lee, K.-H. Chung, S.-J. Koo, J.-H. Kim, *J. Agric. Food Chem.* **2013**, *61*, 9285–9292.
[6] a) A. R. Minter, A. A. Fuller, A. K. Mapp, *J. Am. Chem. Soc.* **2003**, *125*, 6846–6847; b) A. A. Fuller, B. Chen, A. R. Minter, A. K. Mapp, *J. Am. Chem. Soc.* **2005**, *127*, 5376–5383.
[7] D. Bonne, L. Salat, J.-P. Dulcère, J. Rodriguez, *Org. Lett.* **2008**, *10*, 5409–5412.
[8] H. Choe, H. Cho, H.-J. Ko, J. Lee, *Org. Lett.* **2017**, *19*, 6004–6007.
[9] a) T. Yoshimitsu, R. Nakatani, A. Kobayashi, T. Tanaka, *Org. Lett.* **2011**, *13*, 908–911; b) T. Nomura, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2018**, *20*, 119–121.
[10] a) J. W. Bode, N. Fraefel, D. Muri, E. M. Carreira, *Angew. Chem.* **2001**, *113*, 2128–2131; *Angew. Chem. Int. Ed.* **2001**, *40*, 2082–2085; b) J. W. Bode, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 3611–3612; c) J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, *66*, 6410–6424; d) L. D. Fader, E. M. Carreira, *Org. Lett.* **2004**, *6*, 2485–2488; e) N. Lohse-Fraefel, E. M. Carreira, *Org. Lett.* **2005**, *7*, 2011–2014; f) D. Muri, N. Lohse-Fraefel, E. M. Carreira, *Angew. Chem.* **2005**, *117*, 4104–4106; *Angew. Chem. Int. Ed.* **2005**, *44*, 4036–4038; g) N. Becker, E. M. Carreira, *Org. Lett.* **2007**, *9*, 3857–3858; h) N. Lohse-Fraefel, E. M. Carreira, *Chem. Eur. J.* **2009**, *15*, 12065–12081.
[11] D. P. Curran, *J. Am. Chem. Soc.* **1982**, *104*, 4024–4026.
[12] J. D. Low, M. D. Bartberger, Y. Cheng, D. Whittington, Q. Xue, S. Wood, J. R. Allen, A. E. Minatti, *Bioorg. Med. Chem. Lett.* **2018**, *28*, 1111–1115.
[13] R. Sun, Y. Li, L. Xiong, Y. Liu, Q. Wang, *J. Agric. Food Chem.* **2011**, *59*, 4851–4859.
[14] For an excellent overview on the synthesis of isoxazolidines, isoxazolines, isoxazoles: E. Julien, B. Veronique, C. Janine, *Lett. Org. Chem.* **2018**, *15*, 365–374.
[15] a) K.-Y. Dong, H.-T. Qin, F. Liu, C. Zhu, *Eur. J. Org. Chem.* **2015**, 1419; b) S. Yang, H. Li, P. Li, J. Yang, L. Wang, *Org. Biomol. Chem.* **2020**, *18*, 715–724; c) X. Li, Y. Ding, L. Qian, Y. Gao, X. Wang, X. Yan, X. Xu, *J. Org. Chem.* **2019**, *84*, 12656–12663; d) X.-W. Zhang, Z.-F. Xiao, M.-M. Wang, Y.-J. Zhuang, Y.-B. Kang, *Org. Biomol. Chem.* **2016**, *14*, 7275–7281; e) X. Li, X. Wang, Z. Wang, X. Xu *ACS Sustainable Chem. Eng.* **2019**, *7*, 1875–1878; f) C.-H. Yang, Z.-Q. Xu, L. Duan, Y.-M. Li, *Tetrahedron* **2017**, *73*, 6747–6753; g) X. Li, Y. Ding, L. Qian, Y. Gao, X. Wang, X. Yan, X. Xu, *J. Org. Chem.* **2019**, *84*, 12656–12663.
[16] a) P. Nikolaienko, M. Jentsch, A. P. Kale, Y. Cai, M. Rueping, *Chem. Eur. J.* **2019**, *25*, 7177–7184; b) G. S. Kumar, A. Peshkov, A. Brzozowska, P. Nikolaienko, C. Zhu, M. Rueping, *Angew. Chem.* **2020**, *132*, 6575–6581; *Angew. Chem. Int. Ed.* **2020**, *59*, 6513–6519; c) C. Zhu, H. Yue, P. Nikolaienko, M. Rueping CCS, *Chem.* **2020**, *2*, 179–190; d) M. Ghosh, V. S. Shinde, M. Rueping, *Beilstein J. Org. Chem.* **2019**, *15*, 2710–2746; e) C.

Zhu, A. Kale, H. Yue, M. Rueping, *JACS Au* **2021**, *1*, doi.org/10.1021/jacsau.1c00148 .
[17] I. B. Krylov, S. A. Paveliev, A. S. Budnikov, A. O. Terent'ev, *Beilstein J. Org. Chem.* **2020**, *16*, 1234–1276.
[18] Synthesis of 3,5-disubstitued isoxazoles: H.-L. Xiao, C.-C. Zeng, H.-Y. Tian, L.-M. Hu, R. D. Little, *J. Electroanal. Chem.* **2014**, *727*, 120–124.
[19] a) Y. Ashikari, A. Shimizu, T. Nokami, J.-i. Yoshida, *J. Am. Chem. Soc.* **2013**, *135*, 16070–16073; b) S. Song, X. Sun, X. Li, Y. Yuan, N. Jiao, *Org. Lett.* **2015**, *17*, 2886–2889; c) J. Shi, X.-D. Tang, Y.-C. Wu, J.-F. Fang, L. Cao, X.-Y. Chen, Z.-Y. Wang, *RSC Adv.* **2016**, *6*, 25651–25655.

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