A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202012209

Link to VoR: https://doi.org/10.1002/anie.202012209

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10.1002/anie.202012209

RESEARCH ARTICLE

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Electrochemically Tuned Oxidative [4+2] Annulation and Dioxygenation of Olefins with Hydroxamic Acids

Bang-Yi Wei,† Dong-Tai Xie,† Sheng-Qiang Lai, Yu Jiang, Hong Fu, Dian Wei, and Bing Han*

***Abstract**: This work represents the first [4+2] annulation of hydroxamic acids with olefins for the synthesis of benzo[c][1,2]oxazines scaffold via anode-selective electrochemical oxidation. This protocol features mild conditions, oxidant free, high regioselectivity and stereoselectivity, broad substrates scope of both alkenes and hydroxamic acids, and is compatible with terpenes, peptides as well as steroids. Significantly, the dioxygenation of olefins employing hydroxamic acid is also successfully achieved by switching the anode material under the same reaction conditions. The study not only reveals a new reactivity of hydroxamic acids and its first application in electrosynthesis but also provides a successful example of anode material-tuned product selectivity.*

Introduction

1,2-Oxazinane and benzo[c][1,2]oxazine structural motifs[1] as one of important N-O heterocycles constitute the core scaffold of natural products and drugs; selected natural products and drugs containing such moieties are depicted in Figure 1.[2] On the other hand, the reductive cleavage of N-O bond of such rings provides a facile method access to important synthon δ-alkamine.[3] Thus, the efficient synthesis of 1,2-oxazinane and benzo[c][1,2]oxazine has attracted much attention from organic chemists and pharmacologists.[1,4] Among them, taking advantage of Diels-Alder reaction between nitroso hydrocarbons and dienes has become a convenient and powerful method to gain access to 1,2-oxazinanes[5] (Scheme 1a). However, the synthesis of benzo[c][1,2]oxazine using nitrosobenzenes as 4π donors to react with olefins has been difficult to achieve.[6] Until very recently, Liu reported the first nitroso-Povarov reaction of nitrosobenzenes and substituted cyclopentadienes using vinylallenes as the substrates under co-catalysis of gold and silver (Scheme 1b).[6b] Although the elegant work has been reported, it still requires noble metals and structurally special alkenes and does not apply to ordinary alkenes such as styrenes. Thus, the development of practical [4+2] protocol toward benzo[c][1,2]oxazine by exploring new counterpart of nitrosobenzene to react with abundant simple alkenes is urgent demanded.

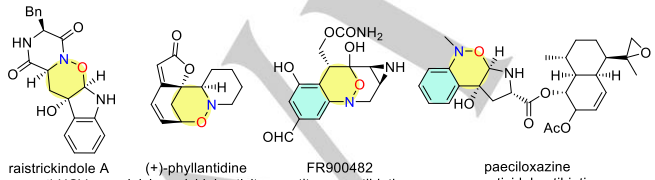
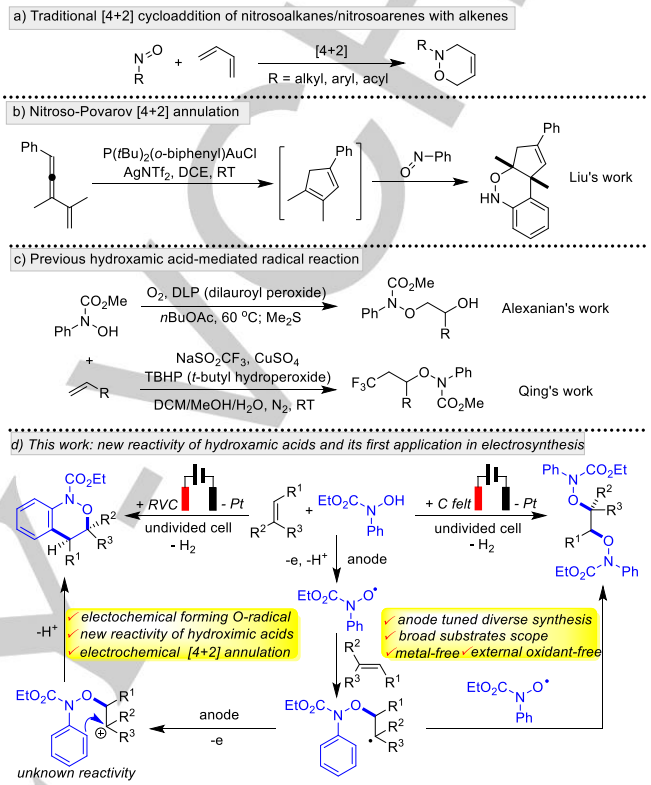


Figure 1. Representative bioactive natural products and drugs.



Scheme 1. Synthetic strategies toward 3,4-dihydro-1H-benzo[c][1,2]oxazines and the application development of hydroxamic acids.

Hydroxamic acid, a readily accessible precursor, has proven to be oxidized to amidoxyl radical which not only serves as an attacking species to add onto olefins, but also acts as a trap to intercept carbon-centered radicals.[7] For example, Alexanian reported a remarkable amidoxyl radical-promoted dioxygenation of alkenes using hydroxamic acids as the partner and oxygen as the oxidant as well as the radical trap (Scheme 1c).[7c] Thereafter, Qing reported an interesting oxytrifluoromethylation of olefins utilizing the in situ generated amidoxyl radical as the C-radical interceptor (Scheme 1c).[7d] In this context, we supposed that the C-radicals derived from intermolecular addition of amidoxyl radicals onto olefins can further be oxidized to the corresponding carbocation under suitable conditions, and the latter experiences a subsequent intramolecular electrophilic substitution with phenyl moiety of hydroxamic acids would provide benzo[c][1,2]oxazines (Scheme 1d). Unfortunately, we are aware of no example wherein hydroxamic acids are employed as the 4-atom-center partner with alkenes in a [4+2] annulation. Such situation may be caused by the strong trapping capacity of amidoxyl radicals to suppress the further oxidation of C-radical as aforementioned. Based on our continuous interest in radical reaction,[8] we report herein a novel reactivity of hydroxamic acids by its anode material-tuned [4+2] annulation with olefins under mild, metal-free, and terminal oxidant-free electrochemical oxidative

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conditions (Scheme 1d). Consequently, a series of monocyclic, fused cyclic and bridged cyclic 3,4-dihydro-1H-benzo[c][1,2] oxazines are efficiently synthesized with excellent regioselectivity and stereoselectivity. Alternatively, the selective electrochemical dioxygenation of olefins with hydroxamic acids can be also realized by simple replacing the anode material under the same reaction conditions (Scheme 1d).

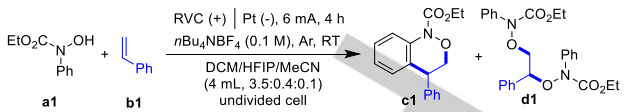
Electrochemical organic synthesis has been revitalized in recent years because it represents one of environmentally friendly and sustainable chemistry which has the advantage of terminal oxidant-free.[9] Although lots of electrochemical oxidative reactions such as difunctionalization,[10] oxidative cycloaddition and annulation of alkenes[11] as well as C-H oxygenation of alkanes[12] have been established, those protocols are focused on the oxidative initiation of C-centered radicals[13] and N-centered radicals.[14] The generation of oxygen-centered radicals[15] and it participated reactions are not appreciated it deserved, especially in intermolecular addition reactions. In addition, with the development of electrode materials,[16] the use of different kinds of electrodes also provides the feasibility for the diversity of electrochemical organic synthesis. In this regard, the tactic not only realizes the first application of hydroxamic acids in organic electrosynthesis,[15a] but also represents the few successful example of both electrochemical O-radical triggered cascade reaction and electrode material-tuned product selectivity.[16e,f]

Results and Discussion

With the conjecture in mind, we commenced the electrochemical oxidative [4+2] annulation of hydroxamic acid **a1** with styrene **b1**. After a comprehensive optimization of reaction conditions by change of electrodes, electrolytes, solvents, and currents, the optimal conditions for [4+2] annulation was obtained. By employing an undivided cell furnished with a reticulated vitreous carbon (RVC) anode and a Pt cathode, the desired [4+2] annulation product **c1** was obtained in 76% yield after a 6 mA constant current electrolysis in mixed solvents of DCM/HFIP/MeCN (4 mL, volume ratio: 3.5/0.4/0.1) under Ar atmosphere for 4 hours at room temperature (Table 1, Entry 1). The anode material was crucial for an efficient [4+2] annulation of both selectivity and yield. The replacement of RVC anode by Pt, C rod, and C cloth gave a mixture of **c1** accompanied with the styrene dioxygenated product **d1** in a combined yields between 39% to 69% with a ratio from 1.6:1 to 3.7:1 (Table 1, Entries 2-4). Significantly, when C felt was used as anode, the reaction gave **d1** as sole product in 81% yield (Table 1, Entry 5). The change of cathode had little effect on the reaction, both Cu and Ni cathodes could provide **c1** as sole product, despite in a bit of lower yields (Table 1, Entries 6 and 7). The change of solvent burden ratio would also reduce the selectivity and yield of **c1** to some extent (Table 1, Entries 8-10). The remarkable decrease of yield of **c1** was observed by use of nBu$_4$NPF$_6$, nBu$_4$NClO$_4$, and Et$_4$NBF$_4$ instead of nBu$_4$NBF$_4$ (Table 1, Entries 11-13). The increase or decrease of electrolytic current leaded lower yields of **c1**, and no reaction took place under the conditions of without current (Table 1, Entries 14-16).

With the optimal conditions established (Table 1, Entry 1), we began to evaluate the substrates scope of olefins by subjecting

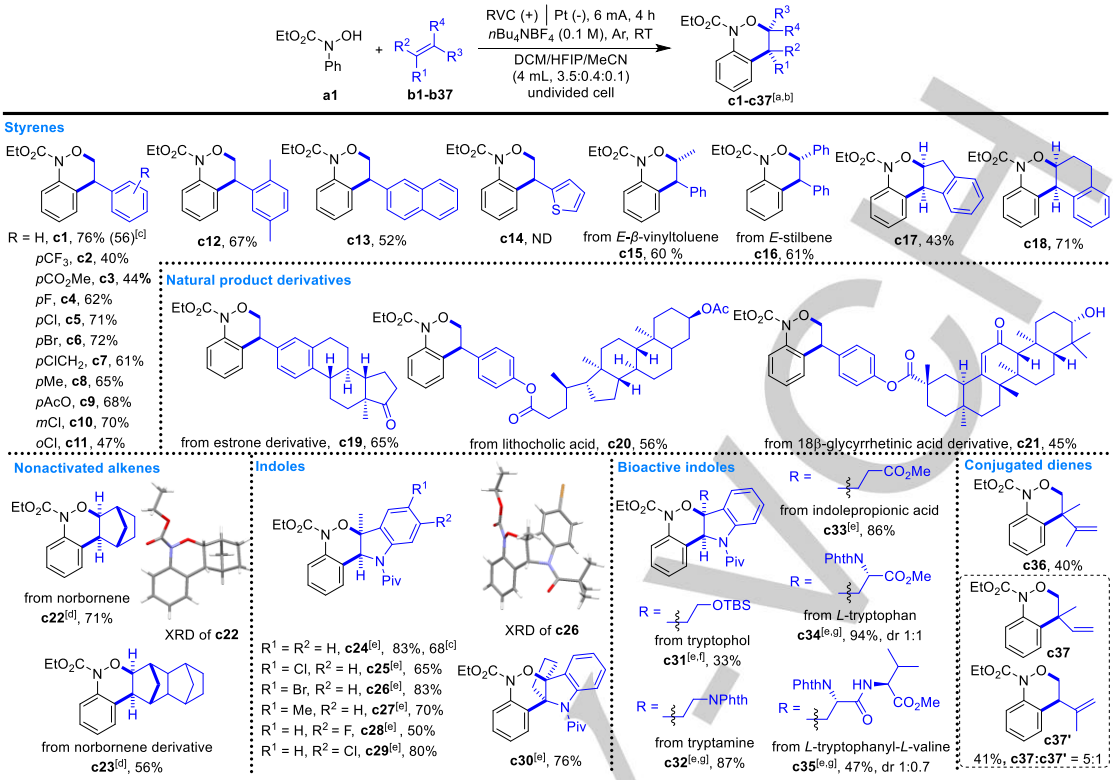
Table 1. Optimization of the Reaction Conditions.[a]



Entry	Variation of conditions	Yield[%][b] c1	d1
1	none	76	0
2	Pt (+) instead of RVC (+)	27	12
3	C cloth (+) instead of RVC (+)	37	10
4	C rod (+) instead of RVC (+)	43	26
5	C felt (+) instead of RVC (+)	0	81
6	Ni (-) instead of Pt (-)	72	0
7	Cu (-) instead of Pt (-)	65	0
8	DCM/HFIP/MeCN (3.5:0.3:0.2)	58	< 5
9	MeCN/HFIP (3.5:0.5)	48	15
10	DCM/HFIP (3.5:0.5)	71	trace
11	nBu$_4$NPF$_4$ instead of nBu$_4$NBF$_4$	50	0
12	nBu$_4$NClO$_4$ instead of nBu$_4$NBF$_4$	42	0
13	Et$_4$NBF$_4$ instead of nBu$_4$NBF$_4$	46	0
14	4 mA, 6 h instead of 6 mA, 4 h	64	0
15	8 mA, 3 h instead of 6 mA, 4 h	34	0
16	without current	0	0

[a] Reaction conditions: RVC anode (100 PPI, 10 mm × 10 mm × 5 mm), Pt cathode (10 mm × 10 mm), constant current = 6 mA, **a1** (0.3 mmol), **b1** (0.6 mmol, 2 equiv.), nBu$_4$NBF$_4$ (0.4 mmol), solvent (DCM/HFIP/MeCN = 3.5 mL/0.4 mL/0.1 mL), undivided cell, Ar, 4 h (3.0 F mol^{-1}). [b] Isolated yields. DCM = dichloromethane, HFIP = hexafluoroisopropanol.

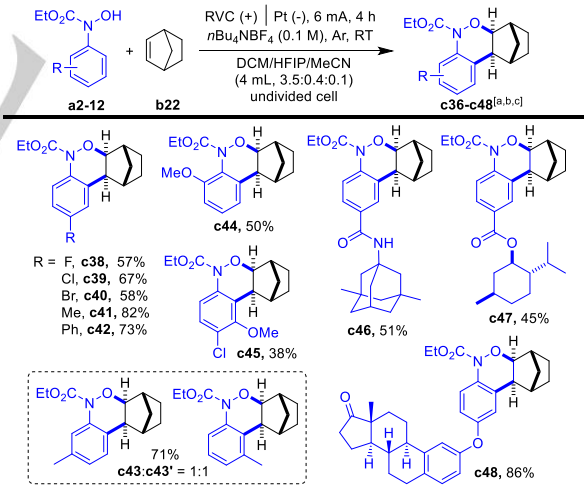
to hydroxamic acid **a1**, and the results are illustrated in Scheme 2. 4-Position substituted styrenes bearing either electron-withdrawing groups such as CF_3, CO_2Me, F, Cl, Br or electron-donating groups such as $ClCH_2$, Me, AcO were all well compatible with this protocol, delivering the desired benzo[c][1,2] oxazines **c2**-**c9** in good yields. 3-Chlorostyrene was also transformed smoothly to **c10** in 70% yield in the protocol. When 2-Chlorostyrene participated in the reaction, the corresponding product **c11** was generated in 47% yield, exhibiting a slight of steric effects. For 2,5-dimethyl styrene, this method generated the corresponding product **c12** in 67% yield. Similarly, 1-naphthyl ethylene was also converted smoothly in the reaction, affording **c13** in 52% yields. Unfortunately, 2-vinylthiophene was inert in the reaction and the desired [4+2] product **c14** was not obtained. (*E*)-1-Propenylbenzene and (*E*)-1,2-diphenylethene were good candidates for the approach as well, producing stereospecific *trans*-product **c15** and **c16** in good yields. Introducing cyclic olefins indene and 1,2-dihydro-naphthalene in this strategy was also successful, as demonstrated in the cases of **c17** and **c18**, in which the *cis*-fused bicyclic products were obtained in 43% and 71% yields, respectively. This protocol enabled styrene incorporated steroid and triterpene such as estrone, lithocholic acid, and 18β-glycyrrhetinic acid derivatives to undergo the [4+2] annulation very well, providing benzo[c][1,2]oxazine tethered complex products **c19**-**c21** in 65%, 56%, and 45% yields, respectively. Besides activated olefins, nonactivated norbornene and its derivatives were good partners with hydroxamic acid as well, giving rise to the merged polycyclic products **c22** and **c23** in good yields with



Scheme 2. Scope of hydroxamic acids. [a] Reaction conditions, see note [a] in Table 1. [b] Isolated yields. [c] The reaction was conducted on 10 mmol scale. [d] Olefin (5 equiv.) was used. [e] Piv = Pivaloyl. [f] TBS = *tert*-Butyldimethylsilyl. [g] Phth = Phthalyl.

exclusive *cis*- and *exo*-selectivities. In addition, indoles with different substituents at various positions were also successfully converted to the desired fused products **c24-c29** in excellent yields with exclusive regioselectivity and stereoselectivity. The structures of **c22** and **c26** were confirmed by X-ray single-crystal diffraction. Notably, this tactic was also suitable for constructing bridged products by employing bicyclic olefin 1,2,3,4-tetrahydrocyclopenta[b]indole, as demonstrated in the case of **c30**. Significantly, bioactive indole derivatives such as tryptophol, tryptamine, indole propionic acid, L-tryptophan and its dipeptide L-tryptophanyl-L-valine were all participated well in the procedure, generating the corresponding products **c31-c35** in good to excellent yields. In addition, conjugated dienes such as 2,3-dimethyl-1,3-butadiene and isoprene were also compatible with this protocol. The former formed **c36** in 40% yield and the later gave a 5:1 mixture of regioisomers of **c37** and **c37'** in combined yields of 41%.[17] The successfully achievement of gram-scale preparation of **c1** and **c24** in 56% (1.60 g) and 68% (2.69 g) yields by constant current electrolyzing 10 mmol of **a1** with the corresponding alkenes, respectively, promised the practicality and availability of this protocol.

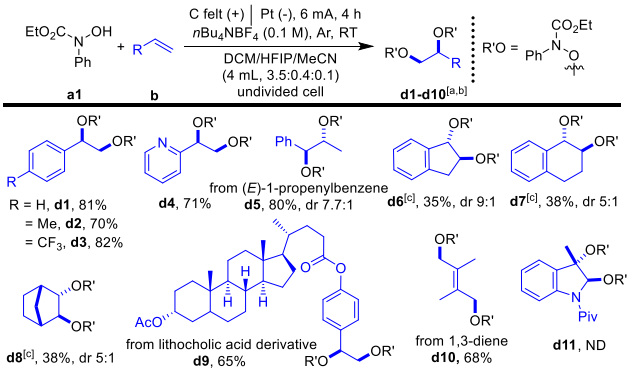
After completing the survey of applicability of olefins, we shift our attention to investigate the scope of hydroxamic acids by matching with norbornene. As shown in Scheme 3, hydroxamic acids bearing substituents with a variety of electronic properties at 4-position on the phenyl moiety were all tolerated in the reaction and produced **c38-c42** in good yields. When 3-methyl hydroxamic acid was involved in the reaction, positional isomers **c43** and **c43'** were obtained in a



Scheme 3. Scope of hydroxamic acids. [a] Reaction conditions, see Entry 1 in Table 1. [b] Olefin (5 equiv.) was used. [c] Isolated yields.

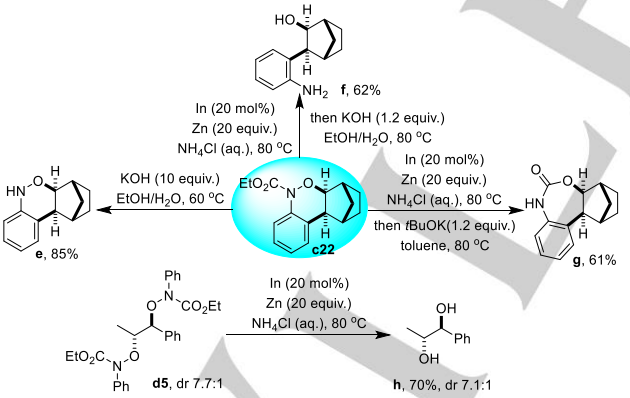
combined yield of 71% with a ratio of 1:1. 2-Methoxyl hydroxamic acid also gave the corresponding product **c44** in 50% yield. This protocol also made promise for 2,4-disubstituted hydroxamic acid, affording the product **c45** as a single isomer. Drugs and natural products such as amantadine, menthol, and estrone tethered hydroxamic acids were also tolerated well with this tactic, as demonstrated in the cases **c46-c48** which provide the desired products in good yields.

Considering that difunctionalization of olefins is an important way for the conversion of C=C double bond,[10] we also realized dioxygenation of olefins using hydroxamic acid by simple switching the anode from RVC to C felt. As shown in Scheme 4, the dioxygenation of representative olefins proceeded very well except indole which was unsuitable under the present conditions, affording products **d1-d10** in moderate to good yields with good stereoselectivity.



Scheme 4. Dioxygenation of representative olefins. [a] Isolated yield. [b] Reaction conditions, see Entry 5 in Table 1. [c] *n*Bu4NOAc was used as the electrolyte.

In order to display the versatile usefulness of products, their several follow-up transformations were conducted (Scheme 5). Hydrolysis of **c22** delivered **e** in 85% yield. Reductive cleavage of N-O bond followed by hydrolysis/intramolecular transesterification of **c22** gave alkene arylhydroxylated product **f** and ring expanded product **g** in 62% and 61% yields, respectively. Moreover, by similar reductive cleavage of N-O bond of product **d5**, the alkene dihydroxylation product **h** was obtained in 70% yield.



Scheme 5. Follow-up transformations.

To achieve insights into the reaction mechanism, competition kinetic isotope effect (KIE) experiments were first conducted under the standard reaction conditions. The measured KIE values from the reaction of an equal amount mixture of hydroxamic acid **a1** and deuterated hydroxamic acid **a1-D5** with styrene **b1,** norbornene **b22** and *N*-pivaloyl indole **b24** were 1.0, 1.08, and 1.17, respectively, suggesting that the rate determining step of the reaction does not involve the C-H cleavage of phenyl moiety of hydroxamic acids and

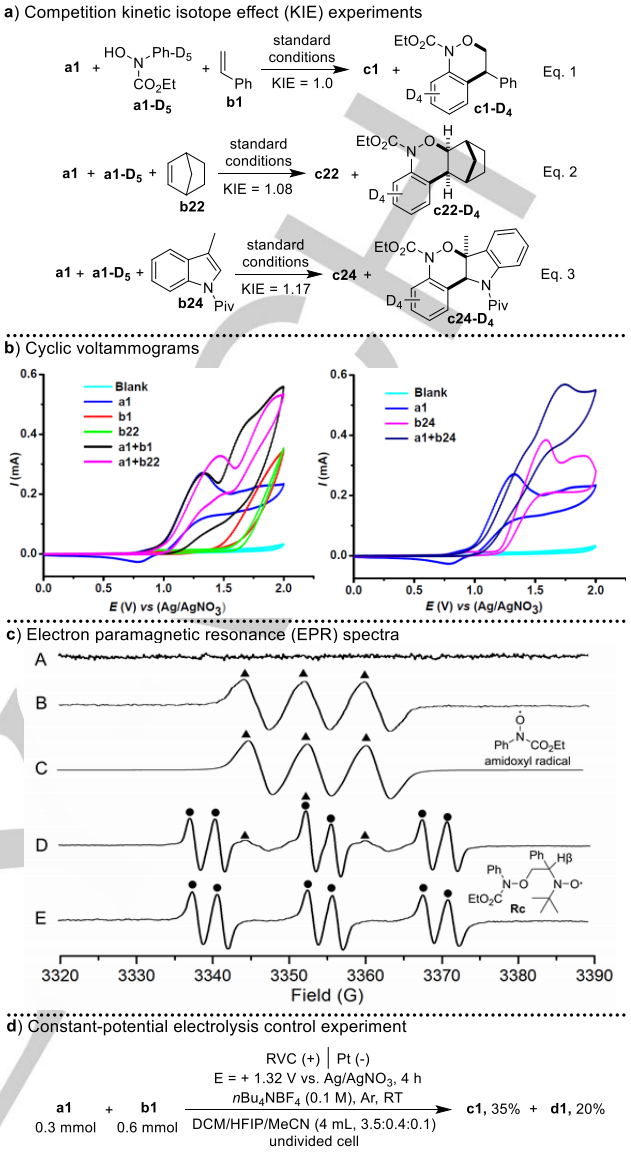


Figure 2. Mechanism studies. (a) Competition kinetic isotope effect (KIE) experiments. (b) Cyclic voltammograms of related compounds (10 mM) in DCM/HFIP/MeCN (volume ratio: 3.5/0.4/0.1) containing 0.1 M *n*Bu4NBF4. Glassy carbon working electrode, Ag/AgNO3 reference electrode, platinum wire counter electrode. Scan rate: 100 mV/s. (c) Electron paramagnetic resonance (EPR) spectra (X band, 9.4 GHz, DCM/HFIP/MeCN, RT) of A): **a1** without electrolysis; B): constant-potential electrolysis of **a1** for 5 min; C): constant-potential electrolysis of **a1** and MNP for 15 min; D) constant-potential electrolysis of **a1**, **b1**, and MNP for 30 min; E) constant-potential electrolysis of **a1**, **b1**, and MNP for 80 min. E = +1.32 V vs. Ag/AgNO3. (d) Constant-potential electrolysis control experiment.

may involve the anodic oxidation of hydroxamic acids (Figure 2a, Eqs. 1-3). Next, cyclic voltammetry (CV) experiments of hydroxamic acid **a1**, styrene **b1**, norbornene **b22**, and *N*-pivaloyl indole **b24** were carried out. An obvious oxidation peak of **a1** could be observed at 1.32 V, whereas no remarkable peak was seen for **b1** and **b22** within 2 V, indicating that **b1** and **b22** cannot be oxidized simultaneously when **a1** is electrochemically oxidized on anode. Obviously, that peak is caused by the anodic single electron oxidation of **a1** to the corresponding amidoxyl radical. In addition, an irreversible reductive peak was observed at 0.78 V in CV experiment of **a1** itself, whereas it was disappeared when **b1**

and **b22** were involved in. These phenomena suggested clearly that amidoxyl radical generated by the anode oxidation of **a1** was intercepted by olefins (Figure 2b, left). Different from **b1** and **b22**, indole type substrate **b24** presented significant oxidation peak at 1.58 V, suggesting that **a1** and **b24** could be simultaneously oxidized on anode in the reaction. Similarly, the reductive peak of amidoxyl radical was not observed in the CV experiment of **a1** with **b24**, manifesting that amidoxyl radical was intercepted by the *in situ* formed indole radical cation (Figure 2b, right). Significantly, the generation amidoxyl radical and its subsequent radical addition onto styrene given by CV studies can also be verified by electron paramagnetic resonance (EPR) experiments (Figure 2c). No EPR signal was obtained when hydroxamic acid **a1** was directly tested without electrolysis, whereas a triplet signal was detected when **a1** was constant-potential electrolyzed at +1.32 V vs. $Ag/AgNO_3$ (Figure 2c, A and B). The triplet signal was assigned as the metastable amidoxyl radical with a_N = 8.03 G and g = 2.0058.[18] When **a1** and the carbon-centered radical spin trap 2-methyl-2-nitrosopropane (MNP) were electrolyzed under the same conditions, only amidoxyl radical triple EPR signal was obtained (Figure 2c, C); however, when styrene **b1** was introduced into in this electrolytic system, the amidoxyl radical triple signal was dramatically decreased and a new set of sextuple signals was obtained (Figure 2c, D). Data analysis indicates that MNP captures a transient C-atom centered radical to produce the metastable aminoxyl radical **Rc** (a_N = 15.31 G, $a_{H\beta}$ = 3.46 G, and g = 2.0060). Apparently, the transient C-radical was derived from the addition of amidoxyl radical onto styrene. With the extension of electrolysis time, the amidoxyl radical triple signal completely disappeared due to the trapping of styrene and finally converted to the sextuple signal of **Rc** (Figure 2c, E). Notably, bulk electrolysis of **a1** and **b1** at the same constant-potential for 4 hours produced the [4+2] product **c1** in 35% yield accompanied with the styrene dioxygenized product **d1** in 20%. This result completely proves that the formation of **c1** and **d1** both undergo the initiation of amidoxyl radical and its radical addition onto styrene; the formed C-radical further experiences intramolecular cyclization on phenyl moiety/intermolecular trapping by another amidoxyl radical would provide the corresponding **c1** and **d1**, respectively. Such conclusions obtained from constant voltage electrolysis control reaction are consistent with those obtained from CV and EPR experiments.

Based on literatures[10g-i] and our observations, the plausible mechanisms for anode selective [4+2] annulation and alkene dioxygenation are postulated as shown in Figure 3. Anode single electron oxidation of hydroxamic acid and subsequent deprotonation produces amidoxyl radical **I**. The interception of radical **I** by olefins yields C-radical **II**. Further oxidation of the latter on anode provides the corresponding carbocation **III** which is then undergoes intramolecular electrophilic substitution (IES) to give annulation products **c1-c23** and **c36-c48** (Figure 3, left). On the other hand, C-radical **II** is trapped by another molecular amidoxyl radical **I** finally to give dioxygenated product **d** when carbon felt is used as the anode (Figure 3, left, in dotted box). One possible reason for such anodic selectivity is that the C-radical is more inclined to further oxidize to carbocation on an RVC electrode than on a C felt electrode. For indole type substrate, since its oxidation potential is similar to that of hydroxamic acid, the anode

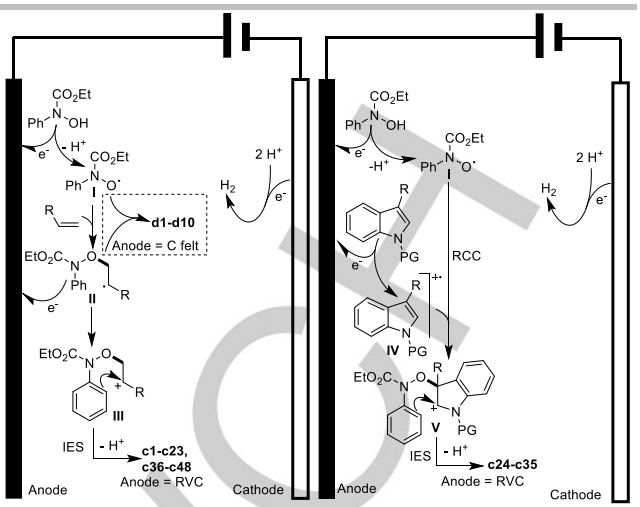


Figure 3. Proposed mechanism.

oxidation of indole and hydroxamic acid takes place simultaneously and produces the corresponding amidoxyl radical **I** and indole cation radical **IV**. The radical cross-coupling (RCC) of those two intermediates generates cation species **V** which immediately experiences the same IES to finally give products **c24-c35** (Figure 3, right).

Conclusion

In summary, we have exploited a novel and facile tactic for the switchable synthesis of 3,4-dihydro-1H-benzo[c][1,2] oxazines and dioxygenated olefins via anode material-tuned selective electrochemical oxidative [4+2] annulation/ dioxygenation of olefins with hydroxamic acids for the first time. The synthetic practicability of this strategy has been demonstrated by the regiospecific and stereoselective production of diverse dioxygenated alkenes and mono, fused cyclic and bridged cyclic 3,4-dihydro-1H-benzo[c][1,2]oxazines as well as by the compatibility with terpenes, peptides and steroids. This terminal oxidant-free protocol not only broadens the new application of hydroxamic acids in synthetic chemistry, but also represents the few successful example of electrochemical triggered O-radical cascade reaction and anode-selective switchable synthetic method. Further research is under way in our laboratory to use hydroxamic acid as a precursor of oxygen free radical for new synthesis purposes.

Acknowledgments

We thank the National Natural Science Foundation of China (Nos. 21873041, 21632001, and 21422205) and the “111” project for financial support. We also thank Prof. Bo Zhou for helpful discussion and proofreading of the first version of manuscript.

Keywords: anode-selective electrosynthesis • annulation • dehydrogenation • heterocycles • oxygen-centred radicals

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annulation. However, allyl benzene gave mixed products which were difficult to isolate and purify. 1-Octene, *n*butyl acrylate, pyrrole, furan, benzofuran, and benzothiophene, on the other hand, were inert in the reaction.

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10.1002/anie.202012209

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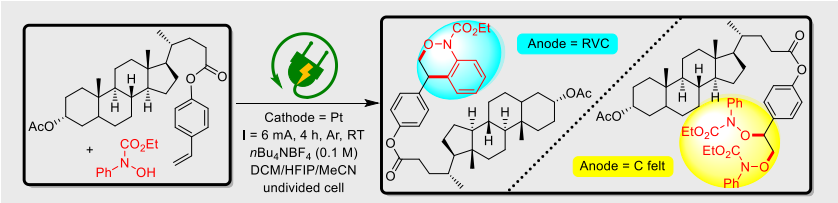

This work represents the first [4+2] annulation of hydroxamic acids with olefins for the synthesis of benzo[c][1,2]oxazines scaffold via anode-selective electrochemical oxidation. Significantly, the dioxygenation of olefins employing hydroxamic acid is also successfully achieved by simple switching the anode material under the same reaction conditions. The study not only reveals a new reactivity of hydroxamic acids and its first application in electrosynthesis but also provides a successful example of anode material-tuned product selectivity.

*Bang-Yi Wei, Dong-Tai Xie, Sheng-Qiang Lai, Yu Jiang, Hong Fu, Dian Wei, and Bing Han**

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