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Synthesis of Isoxazolines and Oxazines by Electrochemical Intermolecular [2 + 1 + *n*] Annulation: Diazo Compounds Act as Radical Acceptors

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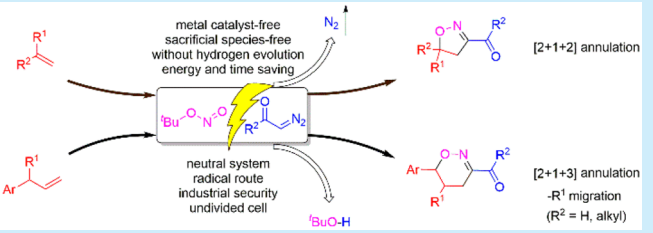
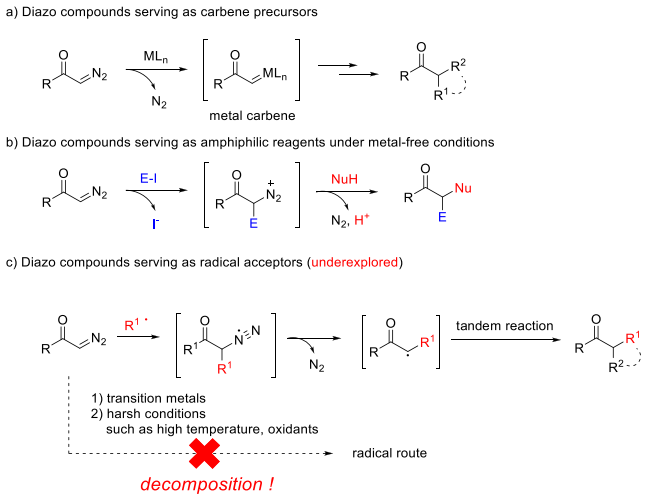
Supporting Information

ABSTRACT: Reported herein is an unprecedented synthesis of isoxazolines and oxazines through electrochemical intermolecular annulation of alkenes with *tert*-butyl nitrite, in which diazo compounds serve as radical acceptors. Notably, [2 + 1 + 2] and [2 + 1 + 3] annulations occur when styrenes and allylbenzenes are used as substrates, respectively. The latter reaction undergoes group migration to form more stable radical, manifesting radical route instead of conventional 1,3-dipolar cycloaddition occurs. Moreover, scale-up experiments suggest the potential application value of these transformations in industry.



Diazo compounds, valuable reagents for chemists, have been extensively studied in organic synthesis.[1] Undoubtedly, transition-metal-involved reactions of diazo compounds that afford highly active metal carbene species have occupied the predominant position in recent years (Scheme 1a).[2] On the other hand, diazo compounds, serving as amphiphilic reagents to react with both nucleophiles and electrophiles, have also been widely used as reactants in multicomponent reactions (Scheme 1b).[3] Recently, it has been reported that diazo compounds could also serve as good radical acceptors and form another free radical via the release of dinitrogen to achieve a multicomponent series reaction (Scheme 1c).[4] However, there only exist several reports on such research topics, probably because traditional conditions for generating free radicals, such as transition metals and high temperature as well as stoichiometric amounts of oxidants, easily cause the decomposition of diazo compounds, excluding the radical process of diazo compounds to a large extent. Therefore, it is imperative to develop a mild and green method achieving diazo-involved radical tandem reaction to discover more unknown reactions.

Scheme 1. Reaction Types of Diazo Compounds



Organic electrosynthesis, regarded as an eco-friendly and mild process in which conventional toxic or dangerous oxidants and reductants could be replaced by electrons, thereby avoiding many side reactions and byproducts to acquire the highest reaction efficiency, has been experiencing a rebirth over the past decades.[5] Recently, explosive literature on electricity-induced free radical reactions has been continuously reported.[6] Given the aforementioned consideration, we try to develop an electrochemical strategy to merge free radicals with diazo compounds in a one-pot reaction under mild and metal-free conditions, achieving intermolecular domino reactions.

Nitrogenous heterocycles, such as isoxazolines and 5,6-dihydro-4*H*-1,2-oxazines, the important heterocyclic compounds which have been widely found in pharmaceuticals and natural products, have attracted much attention over the past decades, and enormous efforts have been devoted to exploring the preparation of these structural motifs.[7] In general, current synthetic methods of isoxazolines include

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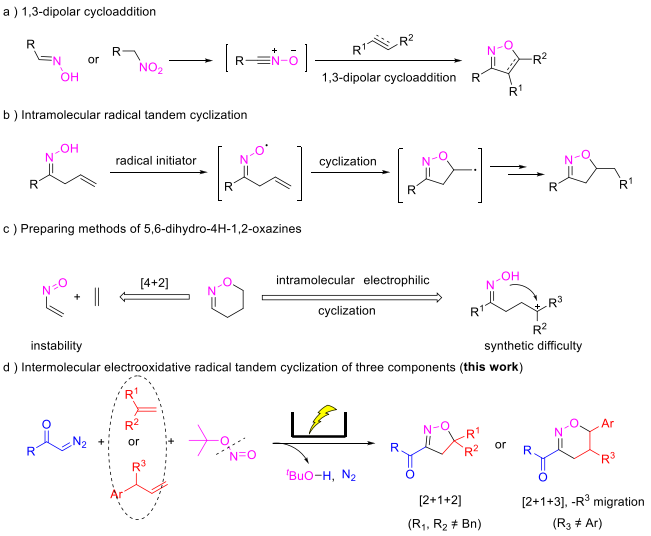
1,3-dipolar cycloaddition of nitrile oxide intermediates to 1,2-dipoles[8] (Scheme 2a) and intramolecular free radical addition

Scheme 2. Synthetic Strategies of Isoxazolines and Oxazines

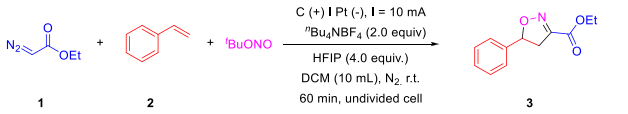


of oximes[9] (Scheme 2b). In contrast, its congener 5,6-dihydro-4*H*-1,2-oxazines have hitherto received scant attention due to lack of convenient and efficient synthetic methods which usually involve intermolecular [4 + 2] cyclization or intramolecular electrophilic cyclizaion (Scheme 2c).[10] In recent years, *tert*-butyl nitrite (^{t}BuONO) has been reported as a good nitroxide donor in the literature.[11] Based on our interest in electrochemical annulation of alkenes,[12] herein, we attempt to achieve the synthesis of isoxazoline and 5,6-dihydro-4*H*-1,2-oxazine derivatives through diazo-involved electrochemical tandem annulation reaction of alkenes with ^{t}BuONO.

To realize the proposed but reasonable transformation, we chose ^{t}BuONO, ethyl diazoacetate (EDA) **1a**, and styrene **2a** as the model substrates to optimize the reaction conditions. To our delight, the desired product **3a** was formed in 78% GC yield under the standard conditions (Table 1, entry 1). Obviously, both decreasing and increasing the current had the negligible impact on the transformation (entries 2−3). After screening a series of electrolytes, we found that some electrolytes like ^{n}BuNPF$_6$ went against the reaction and even prevented the transformation, such as ^{n}BuNOAc (entries 4−5). Notably, a declining reaction yield, 63%, was obtained when hexafluoroisopropanol (HFIP) was removed from the reaction system, and we speculated that HFIP might stabilize the radical intermediates and facilitate the cyclization (entry 6).[12,13] Furthermore, adding some acids or bases as additives could not promote the transformation to some extent (entries 7−8). Thereafter, solvent effect was also investigated in detail, and other common solvents, such as DMF, CH$_3$CN, and DCE, led to the disappointing results (entry 9). In addition, the inferior yields were obtained when rising temperature or reducing temperature (entries 10−11). Moreover, the slight decline of yield was acquired when a nickel plate cathode orc a platinum sheet anode was used (entries 12−13). When the reaction was performed under air, the yield sharply reduced to 58% (entry 14). Expectedly, no product was detected without current passing the reaction system (entry 15).

With the optimal conditions in hand, the substrate scope of reaction in regard to the diazo compounds **1** and alkenes **2** was

Table 1. Optimization of Reaction Conditions[a]



entry	variation from the standard conditions	yield[b] (%)
1	none	78
2	5 mA instead of 10 mA, 120 min	75
3	15 mA omstead of 10 mA, 40 min	75
4	^{n}Bu$_4$NPF$_6$ instead of ^{n}Bu$_4$NBF$_4$	65
5	^{n}Bu$_4$NOAc instead of ^{n}Bu$_4$NBF$_4$	N.D.[c]
6	without HFIP	63
7	adding HOAc as additive	77
8	adding K_2CO_3 as additive	72
9	DMF, CH_3CN, DCE instead of DCM	10−56
10	0 °C instead of r.t. (20−25 °C)	66
11	50 °C instead of r.t. (20−25 °C)	69
12	C (+) I Ni (−) instead of C (+) I Pt (−)	71
13	Pt (+) I Pt (−) instead of C (+) I Pt (−)	63
14	under air	58
15	without electricity	N.D.

[a]Reaction conditions: graphite rod anode (ϕ 6 mm), Pt plate cathode (15 mm × 15 mm × 0.3 mm), constant current = 10 mA, **1a** (0.3 mmol), **2a** (0.6 mmol), ^{t}BuONO (0.9 mmol), ^{n}Bu$_4$NBF$_4$ (0.6 mmol), HFIP (1.2 mmol), DCM (10 mL), rt, 60 min, undivided cell, N$_2$, isolated yield. [b]Determined by GC analysis by using diphenyl as internal standard. [c]N.D. = Not Detected.

explored in Scheme 3. A variety of *para*-substituted styrenes, including alkyl, alkoxyl, aryl, halo, trifluoromethyl, and nitro-substituted styrenes, were smoothly converted to the corresponding products **3a−3j** in considerable yields. Similarly, *ortho*- and *meta*-substituted styrenes were also compatible with the reaction conditions, forming the target products **3k−3n** in moderate yields. Moreover, the desired product **3o** could be acquired from α-methylstyrene in 50% isolated yield. Meanwhile, vinyl-naphthalene derivatives were also suitable substrates in this transformation, furnishing the naphthyl-substituted isoxazoline products **3p** and **3q** in moderate yields. Additionally, steric hindrance of substituted groups was also taken into consideration, and certain multisubstituted styrenes, such as 2,4,6-trimethylstyrene and 2,6-dichlorostyrene, could deliver smoothly the corresponding isoxazoline products **3r** and **3s** in 52% and 50% yields, respectively. As is known to all, it is extremely difficult to achieve the difunctionalization of aliphatic alkenes under metal-free conditions in the electrosynthesis field,[14] perhaps because of the high conversion energy barrier from alkyl radical to alkyl cation. To our delight, aliphatic alkenes, including *gem*-disubstituted alkenes, showed poor reactivity but moderate compatibility under the similar conditions, leading to the corresponding isoxazolines **3t−3w**. However, the method was limited to terminal olefins. As expected, other diazo compounds except diazo amides were also well-tolerated and transformed smoothly to the corresponding products **3x−3z**.

A series of mechanistic studies were carried out to throw light on the reaction mechanism. First of all, cyclic voltammetry (CV) experiments were carried out (Figure 1). An obvious reduction peak of ^{t}BuONO could be observed at −0.85 V (vs Ag/AgCl), while no obvious reduction peaks of other substrates could be detected in their cyclic voltammograms, implying, to a large extent, ^{t}BuONO could be reduced

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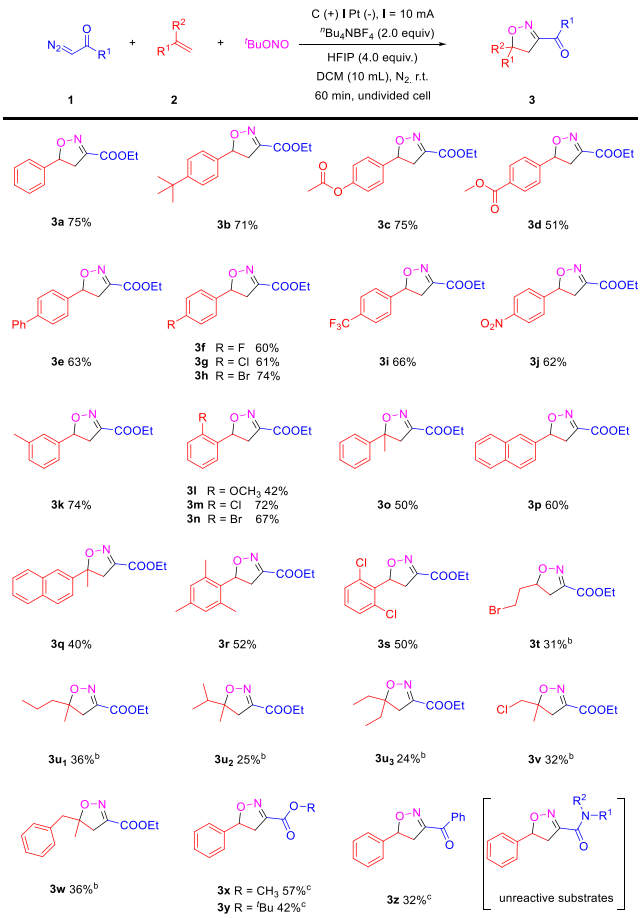
Scheme 3. Synthesis of Isoxazolines[a]



[a]Reaction conditions: graphite rod anode (ϕ 6 mm), Pt plate cathode (15 mm × 15 mm × 0.3 mm), constant current = 10 mA, **1a** (0.3 mmol), **2a** (0.6 mmol), ^{t}BuONO (0.9 mmol), ^{n}Bu$_4$NBF$_4$ (0.6 mmol), HFIP (1.2 mmol), DCM (10 mL), rt, 60 min, undivided cell, N_2, isolated yield. [b]Reaction conditions: graphite rod anode (ϕ 6 mm), Pt plate cathode (15 mm × 15 mm × 0.3 mm), constant current = 10 mA, **1a** (0.9 mmol), **2a** (0.3 mmol), ^{t}BuONO (0.9 mmol), ^{n}Bu$_4$NBF$_4$ (0.15 mmol), HFIP (3.0 equiv), DMF (10 mL), rt, 80 min, undivided cell, N_2, isolated yield. [c]Home-made materials.

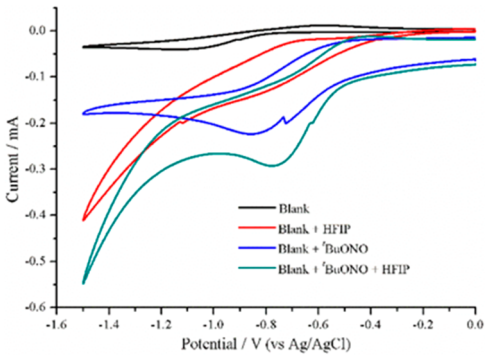
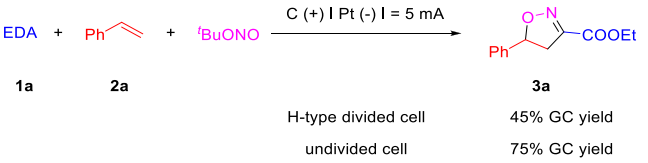


Figure 1. CV experiments.

by capturing an electron at cathode and undergo heterolysis to release an electron-rich nitroso radical and a *tert*-butoxy anion. Notably, HFIP could decrease the reduction potential of ^{t}BuONO to −0.78 V (vs Ag/AgCl) and the result could explain why HFIP could facilitate the transformation. To further clarify the generation of nitroso radical, the model reaction was also executed in a H-type divide cell and the target product **3a** could be detected in 45% GC yield (Scheme 4), indicating that ^{t}BuONO also simultaneously underwent

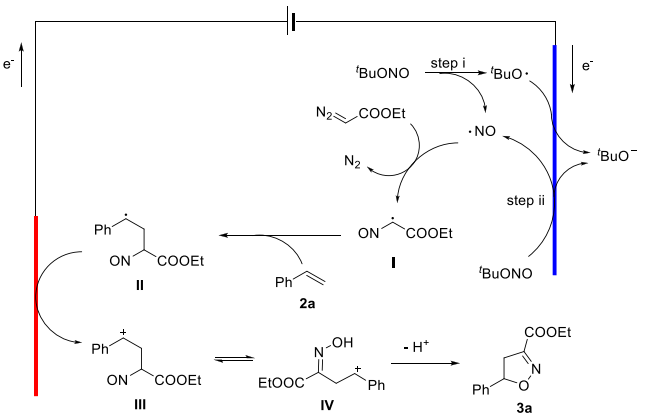
Scheme 4. Control Experiment



homolytic cleavage to form both a nitroso radical and a *tert*-butoxy radical, and the latter species could capture an electron at cathode to form the *tert*-butoxy anion.

Based on the aforementioned results and previously published literature,[4] a mechanism was proposed (Scheme 5). Nitroso radical, resulting from both homolysis and

Scheme 5. Proposed Mechanism for Synthesizing Isoxazolines



heterolysis of ^{t}BuONO, is intermediately intercepted by diazo compounds **1** to afford radical species **I** with the release of nitrogen. Subsequently, the electrophilic C-radical **I** adds to styrene **2a** to deliver the benzylic radical **II**, which is followed by the oxidation of **II** at the anode to produce the benzylic cation **III**. The latter species can further tautomerize to **IV**, which undergoes an intermolecular nucleophilic attack to liberate the molecular target **3a**. At the same time, part of ^{t}BuONO and *tert*-butoxy radical generated through homolytic cleavage captured electrons at the cathode to maintain the electronic conservation.

To fully verify that the transformation underwent a radical route during the whole reaction instead of the 1,3-dipolar cycloaddition process which was achieved by oxidizing intermediate **I** to nitrile oxide intermediate **6** at the anode (Scheme 6, step i).[15] According to the aforementioned proposed mechanism, it was reasonable to speculate whether group migration would occur to form the more stable benzyl radical **VI** from alkyl radical **V** when allylbenzene derivatives **4** were used as substrates instead of styrenes **3**, achieving electrochemical intermolecular [2 + 1 + 3] annulation for the synthesis of 5,6-dihydro-4*H*-1,2-oxazines (Scheme 6, step ii).

With this idea in mind, the optimal conditions were determined after a series of condition screening processes when allylbenzene **4a** was used as a substrate, affording the 5,6-dihydro-4*H*-1,2-oxazine **5a** in moderate isolated yield via a

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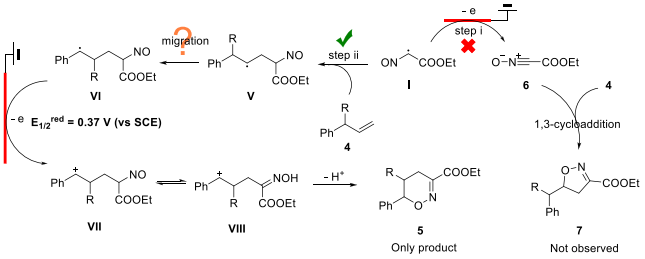
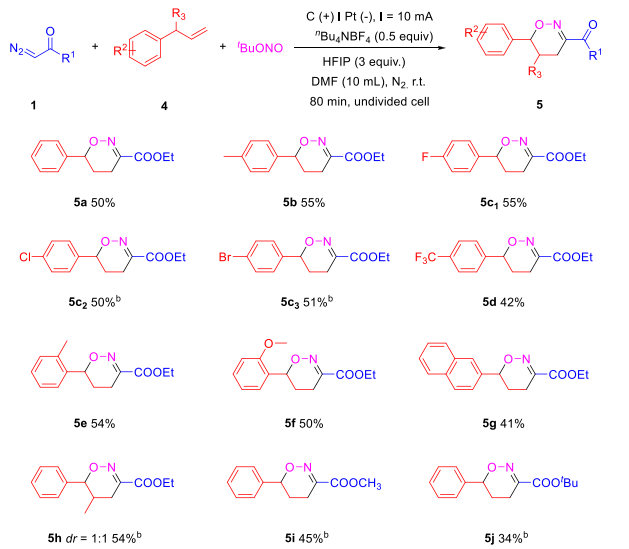
Scheme 6. Proposed Mechanism for Synthesizing 5,6-Dihydro-4*H*-1,2-oxazines



hydrogen migration process, and the substrate scope was shown in Scheme 7. Obviously, *para*-substituted allylbenzenes,

Scheme 7. Synthesis of 5,6-Dihydro-4*H*-1,2-oxazines[a]



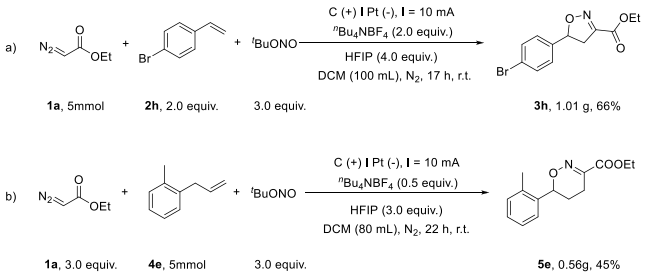
[a]Reaction conditions: graphite rod anode (ϕ 6 mm), Pt plate cathode (15 mm × 15 mm × 0.3 mm), constant current = 10 mA, **1** (0.9 mmol), **4** (0.3 mmol), ^{t}BuONO (0.9 mmol), ^{n}Bu$_4$NBF$_4$ (0.15 mmol), HFIP (3.0 equiv), DMF (10 mL), rt, 80 min, undivided cell, N_2, isolated yield. [b]Home-made materials.

including both electron-donating groups and electron-withdrawing groups, were compatible with the reaction conditions, releasing the desired products **5b**, **5c**, and **5d** in moderate yields. Similarly, some *ortho*-substituted allylbenzene derivatives also showed suitable reactivity and the corresponding products **5e** and **5f** were isolated in 54% and 50% yield, respectively. Reasonably, 2-vinylnaphthalene was tolerated and gave the target product **5g** in 41% isolated yield. It is worth mentioning that the desired product **5h** could be obtained in considerable yield under the standard conditions via methyl group migration. As expected, some similar diazo compounds were also suitable substrates and the corresponding products, such as **5i** and **5j**, could be isolated in passable yields.

To further clarify the potential synthetic application of the protocols, scale-up experiments were carried out (Scheme 8)

To our delight, the considerable isolated yields 66% and 45% were obtained when the gram-scale experiments were performed on 5 mmol by employing 4-bromostyrene **2h** and 2-allyltoluene **4e** as substrates under the respective standard conditions, and the target isoxazoline **3h** could be further converted to the novel antituberculosis agent[7g] via the

Scheme 8. Gram-Scale Synthesis



Buchwald-Hartwig coupling reaction, demonstrating the potential application of these transformations in the field of industry and medicine.

In summary, we have first merged electrosynthesis with diazo compounds to achieve intermolecular free radical [2 + 1 + *n*] annulation of alkenes with ^{t}BuONO via emplaying diazo compounds as radical acceptors. Undoubtedly, the first electrochemical [2 + 1 + 2] annulation is an important complement to conventional synthetic methods of isoxazoline derivatives. To rule out 1,3-dipolar cycloaddition process, we have developed an unprecedented approach for the synthesis of 5,6-dihydro-4*H*-1,2-oxazines by electrochemical [2 + 1 + 3] annulation reactions in which group transfer reactions occurred to generate a more stable intermediate, suggesting the logicality and rationality of the proposed mechanism. Remarkably, adding sacrificial additives and releasing the inflammable and explosive hydrogen, which seem to be the only imperfection of the dehydrogenation electrosynthesis, can be averted in these transformations. In addition, these reactions might have instructive significance in further studies about exploring new reactions using diazo compounds as radical acceptors in organic electrochemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03306.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(15) Similar DFT caculations were provided in part (b), which points out that (1) Radical **I** is expected to be very nucleophilic; (2) the barriers for radical addition are very small; (3) the oxidation of benzylic radicals is feasible owing to their low oxidation potential; (4) the oxidation potential of radical **I** to form nitrile oxide intermediate **6** at the anode is high. However, despite all this, synthesizing isoxazolines via intermolecular radical annulation instead of [3 + 2] cycloaddition has failed to come true. We think the key to the success of our transformation is selective oxidation of electricity. (a) Majek, M.; Jacobi von Wangelin, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 2270. (b) Svejstrup, T. D.; Zawodny, W.; Douglas, J. J.; Bidgeli, D.; Sheikh, N. S.; Leonori, D. *Chem. Commun.* **2016**, *52*, 12302.

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