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Cathode Material Determines Product Selectivity for Electrochemical C–H Functionalization of Biaryl Ketoximes

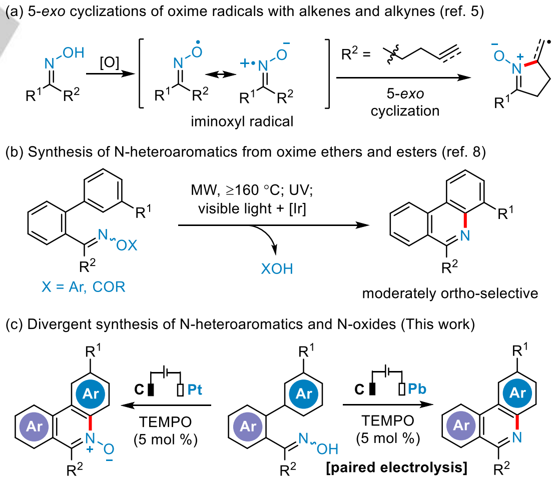
Huai-Bo Zhao,† Pin Xu,† Jinshuai Song, Hai-Chao Xu*

Abstract: The synthesis of polycyclic N-heteroaromatic compounds and their corresponding N-oxides has been developed through electrochemical C–H functionalization of biaryl ketoximes. The oxime substrates undergo dehydrogenative cyclization when a Pt cathode is used, resulting in an unprecedented access to a wide range of N-heteroaromatic N-oxides. The products of the electrosynthesis are switched to the deoxygenated N-heteroaromatics by employing a Pb cathode via sequential anode-promoted dehydrogenative cyclization and cathodic cleavage of the N–O bond in the initially formed N-oxide.

The development of efficient and sustainable C–N bond forming reactions has been a long-standing interest in the field of organic synthesis due to the importance of nitrogen-containing organic molecules for chemistry, biology and materials science.[1] Recently, radical-mediated C–N bond construction has been gaining traction because the relatively high reactivity of the open-shell species provides opportunities for the development of transformations that are difficult using the two-electron manifold.[2] In this context, many research groups have employed the easily available oximes and their derivatives as radical precursors in radical C–N coupling reactions.[3] The cleavage of the O–H bond in oxime produces a σ-type iminoxyl radical with both a reactive oxygen and nitrogen atom.[4] Han and coworkers have demonstrated that iminoxyl radicals can cyclize with alkenes or alkynes to form 5-membered N-heterocyclic compounds (Scheme 1a).[5] However, to the best of our knowledge, similar cyclization reactions with the less reactive arenes have only been mentioned in mechanistic proposals.[6] On the other hand, the thermal or photochemical cleavage of the relatively weak N–O bond in oxime ethers and oxime esters generates an iminyl radical,[3,7] which is reactive toward various π-systems including arenes to afford phenanthridines and some other N-heteroaromatics (Scheme 1b).[8] Although these oxime derivatives are easily prepared, their usage reduces the step and atom economy of the synthetic method.

The ever-increasing demand for safe and sustainable synthetic methods has fueled a rapid growth of organic electrochemistry, which employs traceless electrons as redox reagents.[9] We and a few other research groups have achieved oxidative C–N bond formation facilitated by the concurrence of anodic oxidation and cathodic H_2 evolution.[10,11] Although these electrochemical methods are certainly of great synthetic value, in most cases only one of the two electrochemical half-reactions generates a product of interest. In contrast, paired electrolysis that results in product formation on both electrodes would be more energy efficient and industrially economical. Examples in this direction are available but remain rare.[12] As excellent examples which are also relevant to our current study, Shono and more recently Waldvogel have reported the electrochemical synthesis of aryl nitriles from aldoximes through sequential anodic oxidation and cathodic reduction.[13]

Given the prevalence of N-doped polycyclic aromatic structures in natural products and bioactive compounds,[14] we report herein the synthesis of polycyclic N-heteroaromatics and their corresponding N-oxides via iminoxyl radical-mediated electrochemical C–H functionalization of biaryl ketoximes (Scheme 1c). An interesting and useful finding in our study is that the choice of cathode material played a key role in determining the reaction outcome. Specifically, electrolysis of the biaryl ketoxime using a Pt-based cathode resulted in its dehydrogenative cyclization and furnished an N-heteroaromatic N-oxide. In contrast, sequential dehydrogenative cyclization/cathodic deoxygenation occurred when a Pb cathode was employed, leading to the formation of a deoxygenated N-heteroaromatic compound.



Scheme 1. Cyclization reactions of oximes and oxime derivatives.

Our first task was to identify optimal conditions for the cyclization of **1** (Tables 1, S1 and S2). Initial screening showed that the best reaction system consisted of TEMPO (5 mol %)[15] and KOH (0.5 equiv) in a mixed solvent of $MeCN/H_2O$ (1:1). Notably, KOH fulfilled a dual role of base and supporting electrolyte, which eliminated the need for additional salt. Under the optimal conditions, the desired N-oxide **2** was obtained in 95% yield after the consumption of 2.2 F mol^{-1} of charge (entry 1). The electrosynthesis of **2** could also be conducted using a

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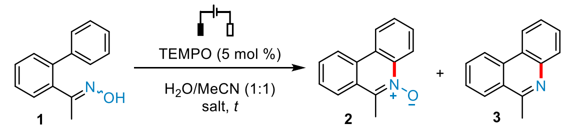
commercially available setup ElectroSyn 2.0 (entry 2). The yield of **2** decreased dramatically in the absence of TEMPO (entry 3) or KOH (entry 4). Interestingly, replacing the Pt cathode with graphite (entry 5), stainless steel (entry 6), red brass (entry 7) or Pb[13b] (entry 8) led to the formation of a mixture of **2** and the corresponding deoxygenated product **3**. Further optimization using Pb cathode showed that the yield of **3** could be boosted to 95% by increasing the charge consumption to 5.5 F mol^{-1} (entry 9) and the reaction temperature to 80 °C (entry 10).[16] Notably, the electrolysis of **1** could be conducted on a decagram scale to afford **2** in 92% yield (entry 11), or **3** in 71% yield (entry 12).

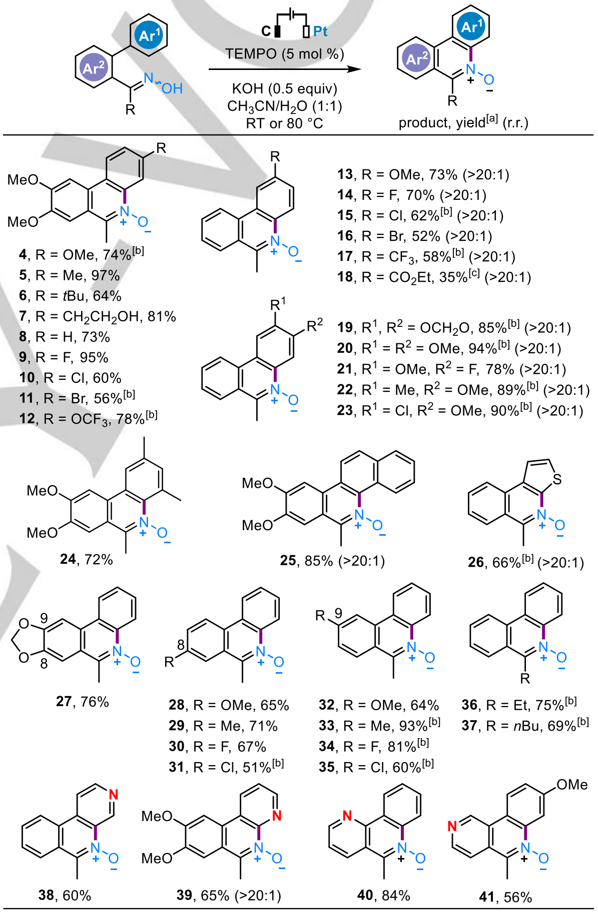
Table 1. Optimization of reaction conditions.[a]



Entry	Salt (0.5 equiv)	Cathode	*t*	Charge (F mol^{-1})	Yield [%][b]		
					2	3	1
1	KOH	Pt	RT	2.2	95[c]	0	0
2[d]	KOH	Pt	RT	2.2	90	0	0
3[e]	KOH	Pt	RT	2.2	14	3	43
4	Na_2SO_4	Pt	RT	2.2	7	0	86
5	KOH	graphite	RT	2.2	47	29	14
6	KOH	stainless steel	RT	2.2	85	6	8
7	KOH	red brass	RT	2.2	59	32	5
8	KOH	Pb	RT	2.2	43	27	14
9	KOH	Pb	RT	5.5	19	54	0
10	KOH	Pb	80 °C	5.5	0	95[c]	0
11	KOH	Pt	RT	2.2	**2**, 92[c] (9.23 g)		
12	KOH	Pb	80 °C	5.2	**3**, 71[c] (6.62 g)		

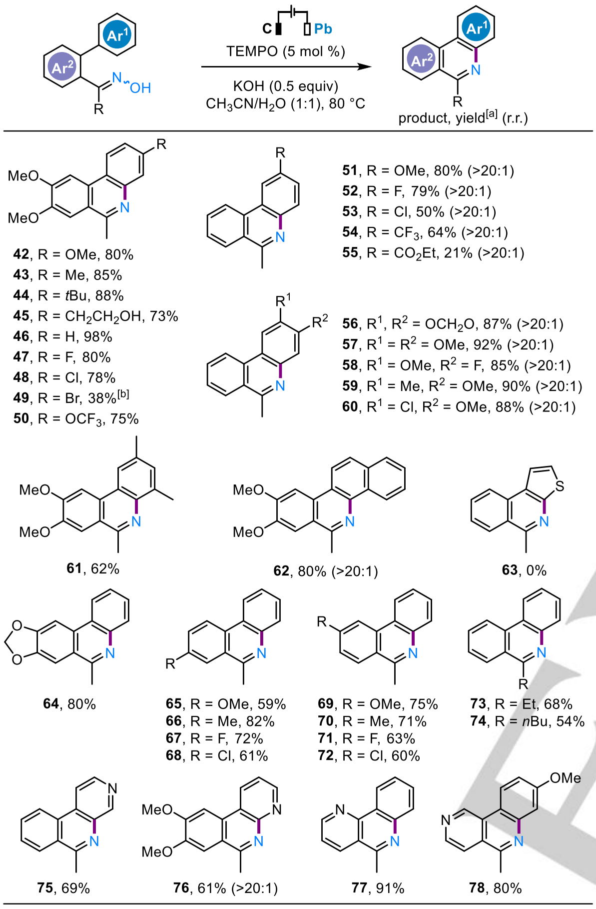
[a] Reaction conditions: Undivided cell, 10 mA, RVC anode ($j \cong 0.16$ mA cm^{-2}), cathode, **1** (0.3 mmol), H_2O (5 mL), MeCN (5 mL), argon. [b] Yield determined by ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [c] Isolated yield. [d] Reaction using ElectroSyn 2.0. [e] No TEMPO.

We next investigated the substrate scope of the electrochemical dehydrogenative cyclization reaction (Scheme 2). The benzene ring Ar^1 of the biaryl oxime could be functionalized with an electronically diverse range of substituents at the position para or meta to the other phenyl group Ar^2 (**4**–**24**). When a meta-substituted substrate was used, the annulation occurred in a regioselective manner at the site para to the functional group on Ar^1 due to mitigated steric hindrance (**13**–**18**). In contrast, previously reported cyclizations that proceeded through sterically less hindered iminyl radical intermediates showed either reduced or no selectivity at all.[8,11a,17] Replacing Ar^1 with another aromatic moiety, such as a 2-naphthalene- or a 3-thiophene substituent, exhibited no detrimental effect on the regioselectivity of the reaction (**25**, **26**). A primary alcohol group was unaffected despite that TEMPO was known to catalyze the electrochemical oxidation of alcohols (**7**).[15a,b] The reaction was also broadly compatible with a variety of functional groups at positions 8 and 9 of aryl ring Ar^2, including OCH_2O (**27**), OMe (**28**, **32**), Me (**29**, **33**), F (**30**, **34**) and Cl (**31**, **35**). The Me on the C-N double bond of the oxime moiety could be substituted by an ethyl (**36**) or *n*-butyl (**37**) group. Finally, phenylpyridine-based substrates were also well tolerated, leading to the formation of aromatic N-oxide products bearing free pyridyl nitrogen atoms (**38**–**41**). These compounds are expected to be difficult for traditional methods that rely on the oxidation of preformed N-heteroaromatic compounds due to chemoselectivity issues. It should be emphasized that the electrochemical cyclization of oximes that form N-oxide products with low solubility in MeCN/H_2O (1:1) needed to be conducted at 80 °C to prevent precipitation on the porous anode and the concomitant electrode passivation.

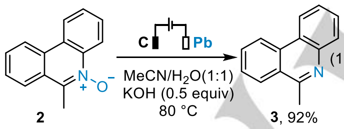


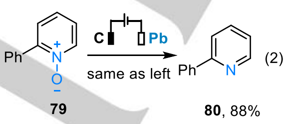
Scheme 2. Substrate scope for the dehydrogenative cyclization. Reaction run with 0.3 mmol of oxime for 1.7–2.7 h (2.1–3.4 F mol^{-1}). [a] Isolated yield, regioisomeric ratio in parenthesis. [b] Reaction at 80 °C. [c] Na_2CO_3 as base.

The dehydrative C–H functionalization reactions (Scheme 3) showed similar substrate scope and regioselectivity as the dehydrogenative cyclization reactions shown above. Exceptions included the occurrence of debromination during the formation of **49** and the failure to form the thiophene-containing compound **63**.

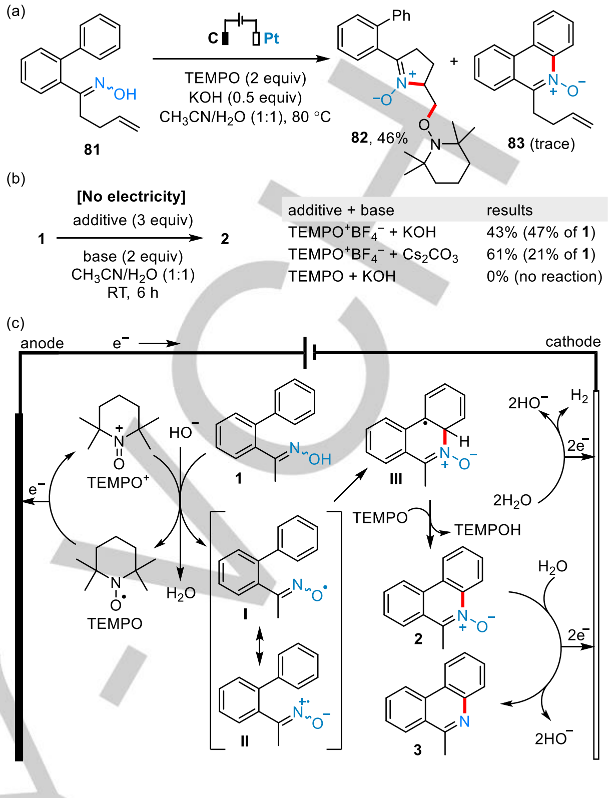


Scheme 3. Substrate scope for the dehydrative cyclization. Reaction run with 0.3 mmol of oxime for 4.0–5.2 h (5.0–6.5 F mol^{-1}). [a] Isolated yield, regioisomeric ratio in parenthesis. [b] 43% of **46** was also obtained.





The deoxygenation of N-oxides generally requires Pd-catalyzed hydrogenation or a stoichiometric amount of a chemical reductant.[18] Our electrochemical reaction provides a highly efficient and clean method for deoxygenating N-oxides. For example, aromatic N-oxides such as **2** and **79** could be efficiently deoxygenated in the absence of TEMPO to afford the desired compounds **3** and **80**, respectively [Eq.s (1) and (2)].



Scheme 4. Mechanistic studies and proposal.

The electrolysis of **81** bearing an alkene in the presence of 2 equiv of TEMPO led to the generation of **82** and a trace amount of **83** (Scheme 4a), suggesting that the reaction with the phenyl group to form a 6-membered ring was much more difficult than the alternative 5-*exo-trig* cyclization with the alkene moiety. These results also lent support to the involvement of an iminoxyl radical intermediate. In addition, the cyclization of **1** into **2** could also be promoted by using 3 equiv of TEMPO$^+$BF$_4^-$, albeit at a lower yield, but not by TEMPO (Scheme 4b). The yield reduction was likely caused by the decomposition of the oxidant under the basic conditions.

A mechanism for the electrochemical cyclization of ketoximes was proposed as follows (Scheme 4c). The electrolysis begins with the anodic oxidation of TEMPO ($E_{p/2}$ = 0.51 V vs SCE) into TEMPO$^+$, which then reacts with **1** ($E_{p/2}$ = 1.39 V vs SCE) to afford an iminoxyl radical (resonance structures **I** and **II**).[19,20] N-Cyclization of the iminoxyl radical onto the phenyl ring,[21] followed by re-aromatization, furnishes the N-oxide **2**. When a Pt cathode is employed, H_2O is cathodically reduced to generate H_2 and HO$^-$. Alternatively, the use of a Pb cathode, which has a higher overpotential for H_2 evolution, would favor the formation of **3** due to the cathodic cleavage of the N–O bond in **2**. Since HO$^-$ is continuously generated at the cathode, only a substoichiometric amount of KOH is needed.

In summary, we have demonstrated that the electrolysis of easily available biaryl ketoximes can lead to the chemo- and regioselective formation of polycyclic N-heteroaromatic N-oxides or the corresponding deoxygenated N-heteroaromatics by employing different cathode materials.

Acknowledgements

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Keywords: electrochemistry • paired electrolysis • radicals • oximes • heterocycles

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[16] The Pb concentration in the reaction solution after electrolysis and in the purified product **3** was determined using atomic absorption spectroscopy (AAS) to be 1.9 ppm and 350 ppm, respectively.

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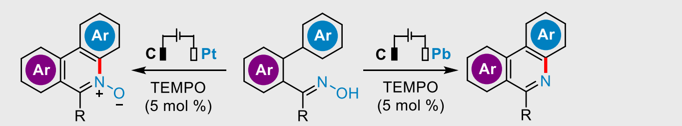
[19] The oxidation of oxime **1** by TEMPO$^+$ has also been confirmed by cyclic voltammetry (Figures S1 and S2). Under galvanostatic conditions in the presence of KOH, it is also possible the oxime **1** is oxidized directed on the electrode, especially considering the low oxidation potential of the conjugate base of the oxime (Figure S3). An example of iminoxy radical formation via direct electrolysis: H.-L. Xiao, C.-C. Zeng, H.-Y. Tian, L.-M. Hu, R. D. Little, *J. Electroanal. Chem.* **2014**, *727*, 120–124.

[20] The cyclic voltammetry experiments (Figure S3) indicated that a small portion of oxime **1** was deprotonated by KOH in H_2O/MeCN (1:1), suggesting that the pKa of **1** in the mixed solvent is close to that of H_2O.

[21] Density functional theory (DFT)-based calculations (M06/2X) suggested the cyclization of the iminoxyl radical to form **III** was endergonic with ΔG = 11.9 kcal mol^{-1}.

COMMUNICATION



☑ Divergent synthesis
☑ Paired electrolysis

☑ Atom economical
☑ Regioselective

A divergent synthesis of polycyclic N-heteroaromatics and the corresponding N-oxides through electrochemical C–H functionalization of biaryl ketoximes has been developed. The product selectivity is controlled easily by the choice of the cathode material.

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