

# Formal Aza-Wacker Cyclization by Tandem Electrochemical Oxidation and Copper Catalysis

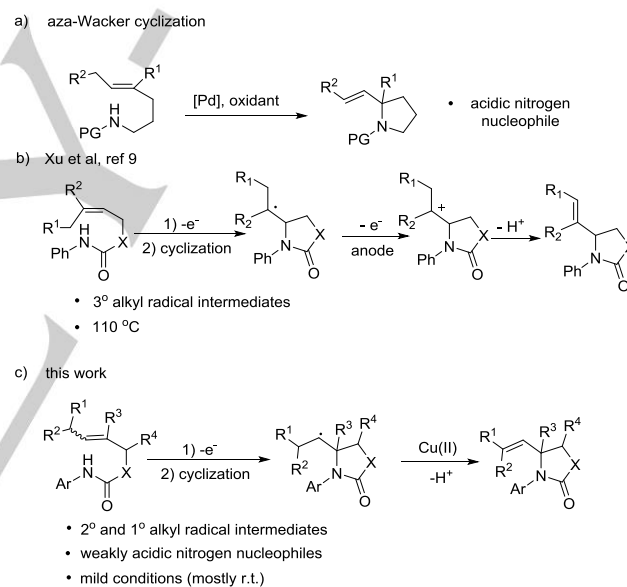
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**Abstract:** In oxidative electrochemical organic synthesis, radical intermediates are often oxidized to cations en route to final product formation. Here we describe an approach to transform electrochemically generated organic radical intermediates into neutral products via reaction with a metal catalyst. This approach combines electrochemical oxidation with Cu catalysis to effect formal aza-Wacker cyclization of internal alkenes. The Cu catalyst is essential for transforming secondary and primary alkyl radical intermediates into alkenes. A wide range of 5-membered N-heterocycles including oxazolidinone, imidazolidinone, thiazolidinone, pyrrolidinone and isoindolinone can be prepared under mild conditions.

Electrochemical organic synthesis has witnessed a renaissance in the last decade.<sup>1</sup> Compared with traditional organic synthesis which uses chemical redox agents, electrochemical synthesis employs electric current which is readily available, waste-free, and potentially renewable. Moreover, the reactivity can be tuned by changing the applied potential in electrochemical synthesis, overcoming the limitations of redox potentials of chemical reagents. In electrochemical oxidations of anionic species, radicals are the most frequent intermediates, which are usually further oxidized to give carbocations en route to final product formation.<sup>2</sup> Trapping radical intermediates by metal complexes is a strategy with a significant potential to expand the scope of electrochemical synthesis.<sup>1g,3</sup> In elegant examples, Lin and co-workers used Mn(III)-N<sub>3</sub> and Mn(III)-Cl complexes to convert alkyl radical intermediates into alkyl azides and chlorides via radical group transfer.<sup>1g,3a,3b</sup> Nevertheless, this strategy remains under-developed. Herein, we describe an approach to use Cu catalysis to convert electrochemically generated alkyl radicals into alkenes, leading to a formal aza-Wacker cyclization of internal alkenes.

Pd-catalyzed aza-Wacker cyclization is an attractive approach to generate nitrogen-containing five-membered heterocycles (Scheme 1a),<sup>4</sup> which are ubiquitous in many natural products and synthetic bio-active compounds.<sup>5</sup> However, Pd catalysis usually works for acidic nitrogen nucleophiles such as sulfonamides (pK<sub>a</sub> = 13-18 in DMSO),<sup>6a,6b</sup> while less acidic substrates like carbamates and amides (pK<sub>a</sub> 20-26)<sup>6</sup> are sluggish reaction partners.<sup>4b,7</sup> A Cu-catalyzed method was developed for a similar transformation of carbamates and ureas, but a high reaction temperature and a strong oxidant (Dess–Martin periodinane) were required.<sup>8</sup> The group of Xu developed an electrochemical protocol of intramolecular oxidative amination of alkenes that avoided the use of chemical oxidants (Scheme 1b).<sup>9</sup> It was

proposed that electrochemical oxidation generated an amidyl radical, which underwent intramolecular cyclization to give an alkyl radical. The latter was oxidized by the electrode to afford alkene moiety upon proton loss. Despite the elegant concept, this method relied on having tertiary alkyl radical intermediates, probably due to inefficient direct oxidation of secondary and primary alkyl radicals at the electrode.<sup>9</sup> Thus, the scope of the method was limited. Additionally, this method still required an elevated temperature (110 °C). Taking advantage of the ability of Cu species to mediate oxidative transformation of alkyl radicals into alkenes,<sup>10</sup> we incorporated Cu catalysis into the electrochemical oxidative amination process (Scheme 1c). This approach enabled, for the first time, the transformation of secondary and even primary alkyl radical intermediates, leading to a broad-scope methodology for formal aza-Wacker cyclization. The Cu catalysis also enabled the reactions at room temperature.



**Scheme 1.** a) Pd-catalyzed aza-Wacker cyclization. b) Electrochemical oxidative amination by Xu et al. c) Tandem electrochemical oxidation and Cu catalysis for formal aza-Wacker cyclization.

We began by investigating the electrochemical oxidative amination of crotyl N-phenylcarbamate **1a** in the presence of a Cu catalyst (Table 1). After initial exploration of conditions, we found that in a divided cell with MeOH as solvent, carbon fiber as working electrode, 0.2 M LiClO<sub>4</sub> as electrolyte, Cu(OAc)<sub>2</sub> (30 mol%) as catalyst, 2 eq. of NaOAc as base, and under constant current (3 mA, *j* = 0.19 mA/cm<sup>2</sup>), the desired product **2a** could be obtained in a yield of 33% after passing 2.2 F electron at room temperature (entry 1, table 1). Increasing the amount of base to 4 eq. increased the yield to 51% (entry 2, Table 1), while without base the reaction could hardly proceed (entry 3, Table 1). The use of NaHCO<sub>3</sub> or LiO<sup>t</sup>Bu as base led to precipitation of Cu salts and low yields (entries 4 and 5, Table 1). The use of NaOPiv (OPiv=

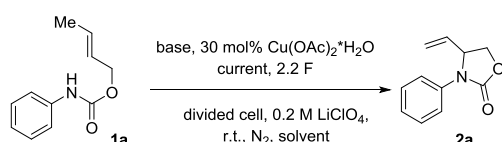
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pivalate), however, improved the yield to 64% (entry 6, Table 1). When the reaction was conducted with a lower current 1.5 mA, the yield was further increased to 70% (entry 7, Table 1). Using reticulated vitreous carbon (RVC) in place of carbon fiber as working electrode decreased the yield to 35% (entry 8, Table 1). The current density at RVC was higher than at carbon fiber (0.25 vs 0.10 mA/cm<sup>2</sup>), which might lead to a higher concentration of radical intermediates that were subject to side reactions. The surface of the RVC is smooth and glass-like, while the surface of carbon fiber is rough and may contain more oxygen functional groups. The different surface nature might be responsible for the different reactivity as well. Consistent with this hypothesis, Pt working electrode was completely incompetent for this reaction (SI). The use of NBu<sub>4</sub>OTs as electrolyte reduced slightly the yield (entry 9, Table 1). As solvent of lower polarity was reported to facilitate Cu-mediated oxidative elimination,<sup>10a</sup> some mixed solvents were tried. A 1:1 mixture of MeOH and dichloromethane (DCM) was the best solvent, giving a yield of 80% (entry 10, Table 1).

**Table 1.** Optimization of conditions for the electrochemical formal aza-Wacker cyclization.



entry	solvent	base	<i>i</i> / mA	yield <sup>[a]</sup> / %
1	MeOH	2 eq. NaOAc	3	33
2	MeOH	4 eq. NaOAc	3	51
3	MeOH	—	3	trace
4	MeOH	4 eq. NaHCO <sub>3</sub>	3	10
5	MeOH	4 eq. LiO <sup>t</sup> Bu	3	10
6	MeOH	4 eq. NaOPiv	3	64
7	MeOH	4 eq. NaOPiv	1.5	70
8 <sup>[b]</sup>	MeOH	4 eq. NaOPiv	1.5	35
9 <sup>[c]</sup>	MeOH	4 eq. NaOPiv	1.5	66
10 <sup>[d]</sup>	MeOH-DCM	4 eq. NaOPiv	1.5	80

Reaction conditions: 0.2 mmol scale, carbon fiber (geometric area 15.8 cm<sup>2</sup>) as anode, Pt foil (1 cm<sup>2</sup>) as cathode; 8 mL solvent in each cell; **1a**, base and catalyst in anodic cell; 0.4 mL additional H<sub>2</sub>O in cathodic cell. <sup>[a]</sup> GC yield. <sup>[b]</sup> RVC cube (geometric area 6 cm<sup>2</sup>) as anode. <sup>[c]</sup> 0.1 M NBu<sub>4</sub>OTs as electrolyte. <sup>[d]</sup> The ratio of MeOH: DCM is 1:1.

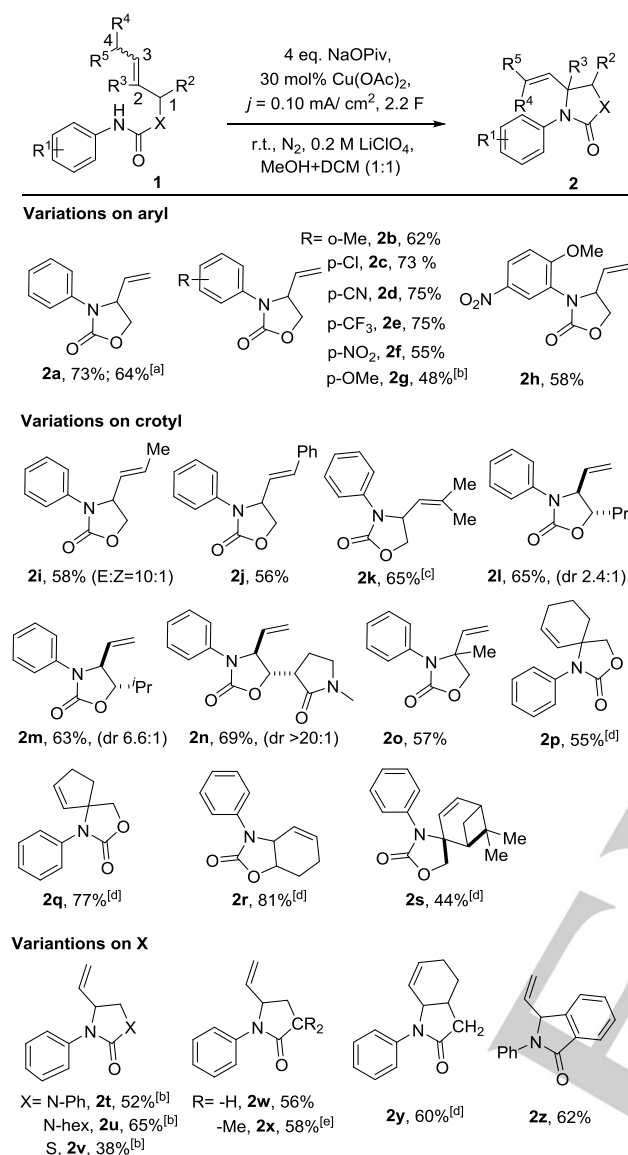
The optimized conditions (entry 10, Table 1) were applied to explore the substrate scope of this transformation (Figure 1). First, substrates with different substituents on the aryl group were tested. *ortho*-Methyl group was tolerated, giving **2b** in 62% yield. Substrates with an electro-withdrawing group at the *para*-position, such as -Cl (**1c**), -CF<sub>3</sub> (**1d**) and -CN (**1e**), were transformed in good yields. The strongly electron-withdrawing nitro group

decreased the yield to 55% (**2f**). With an electron-donating -OMe at the *para* position, oxidation of the arene dominated under the standard conditions, and the cyclization product **2g** was obtained in less than 10% yield. Interestingly, by using NBu<sub>4</sub>OTs as electrolyte, the arene oxidation was suppressed and **2g** was obtained in 48% yield. On the other hand, when both -NO<sub>2</sub> and -OMe were present on the phenyl, the cyclization product (**2h**) was obtained in 58% yield under the standard conditions.

Next, variations on the crotyl part of the substrates were explored. When there was a methyl substituent at the C4 position (Figure 1), an oxazolidinone containing an internal alkene moiety (**2i**) was obtained in 58% yield (E: Z= 10:1). A phenyl group at the C4 position was also tolerated (**2j**). When there are two methyl groups on C4, the reaction also occurred to give **2k** in a decent yield (65%), but in this case heating to 75 °C was necessary. Substitutions at the C1 position were tested using *n*-Pr, *i*-Pr, and *N*-methyl-2-pyrrolidone group. All three substrates gave good yields (**2l**, **2m** and **2n**). The diastereoselectivity (*trans* over *cis*) increases with the steric bulk of the substituent: 2.6:1 for *n*-Pr, 6.6:1 for *i*-Pr, and > 20:1 for *N*-methyl-2-pyrrolidone. When there was a substituent at the C2 position, a quaternary carbon center could be formed during cyclization (**2o** – **2q**, **2s**). Gratifyingly, this protocol enabled the synthesis of spiro structures containing 6-membered (**2p**) and 5-membered (**2q**) cyclic alkene, bicyclic (**2r**), and multicyclic structures (**2s**). It was noted that the cyclization was insensitive to the configuration of the alkene. Thus, the use of substrates as *E/Z* mixture was possible (**1t**, **1v**, **1x** and **1z**).

The substrate scope could be extended beyond carbamates to include ureas (**2u**, **2t**), a carbamothioate (**2v**), and amides (**2w**–**2y**). These reactions yielded valuable 5-membered *N*-heterocycles such as imidazolidinone, thiazolidinone, and  $\gamma$ -lactam. The amide and alkene units in the substrate could be connected by a benzene linker, giving rise to isoindolinone (**2z**) in 62% yield.

While the reactions in Figure 1 were conducted at a scale of 0.2 mmol, the reaction of **1a** was scaled to 6 mmol, and with a reduced amount of catalyst (10 mol%). The target product **2a** was obtained in 64% yield (0.73 g).

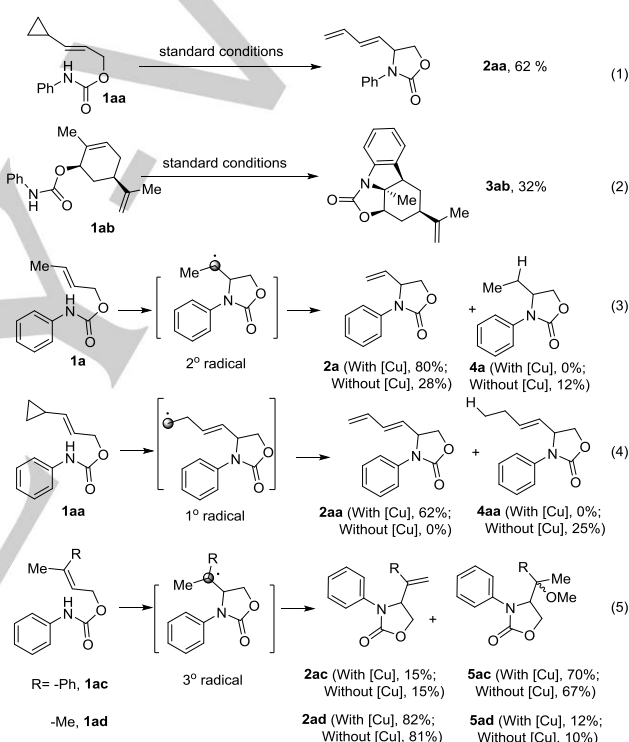


**Figure 1.** Scope of the electrochemical formal aza-Wacker cyclization. Reaction conditions: 0.2 mmol scale, carbon fiber (geometric area 15.8 cm<sup>2</sup>) as anode, Pt foil (1 cm<sup>2</sup>) as cathode; 8 mL solvent in each cell; 1, base and catalyst in anodic cell; 0.4 mL additional H<sub>2</sub>O in cathodic cell. <sup>[a]</sup> In 6 mmol scale, detailed conditions in SI. <sup>[b]</sup> 0.1 M NBu<sub>4</sub>OTf as electrolyte. <sup>[c]</sup> MeOH-PhCl(1:3) as solvent, 0.1 M NBu<sub>4</sub>OTf as electrolyte, 4 eq. NaOAc as base, 75 °C. <sup>[d]</sup> MeOH-PhCl (1:1) as solvent, 0.1 M NBu<sub>4</sub>OTf as electrolyte, 4 eq. NaOAc as base, 65 °C. <sup>[e]</sup> 6 eq. NaOPiv as base, 5 F.

A few experiments were conducted to probe the mechanism of the transformation. For a substrate containing a cyclopropyl group (**1aa**), the product from ring-opening and elimination (**2aa**) was obtained in 62% yield under the standard conditions (eq. 1). This result is consistent with the formation of an alkyl radical after intramolecular cyclization. For a bulky substrate **1ab**, **3ab** was obtained as the major product in 32% yield (eq. 2), which presumably originated from the addition of the alkyl radical into the aryl group.<sup>11</sup>

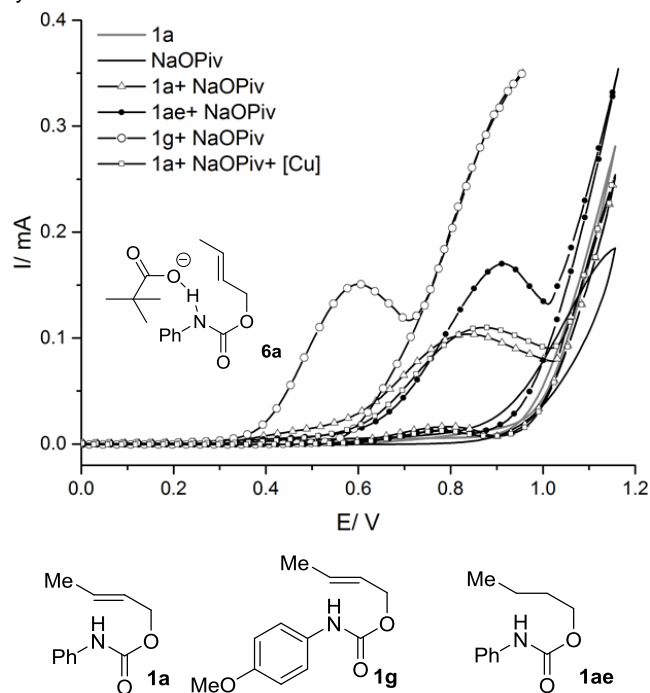
To probe the role of the Cu catalyst, reactions of representative substrates were conducted with and without the Cu(OAc)<sub>2</sub>

catalyst. For substrate **1a**, 80% of **2a**, but no **4a** (formed from a hydrogen abstraction reaction by the alkyl radical)<sup>12</sup> was obtained in the presence of Cu. In the absence of Cu, however, **2a** was obtained only in 28% yield, and the reaction gave 12% of **4a** (eq. 3). For substrate **1aa**, 62% of elimination product **2aa** but no product **4aa** was obtained in the presence of Cu (eq. 4). In the absence of Cu, no **2aa** was obtained. Instead, **4aa** was formed in a yield of 25%. These results indicate that the Cu catalyst is essential for the efficient oxidative elimination of secondary and primary alkyl radical intermediates to form alkenes. Interestingly, for reactions involving tertiary alkyl radicals, for example, for **1ac** and **1ad**, the products were the same between in the presence and absence of the Cu catalyst (eq. 5). This result indicates that the oxidation of tertiary alkyl radicals occurs readily at the electrode even without a Cu catalyst, consistent with the work of Xu and co-workers<sup>9</sup>.



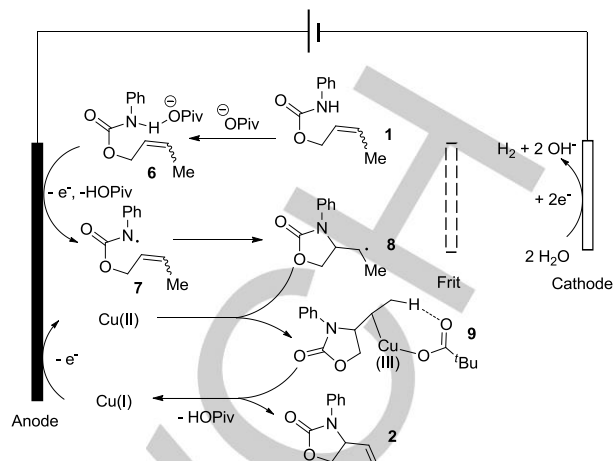
Cyclic voltammetry (CV) was used to probe the oxidation process at the electrode. The direct oxidation of **1a** started only at potentials higher than 1.0 V vs the Fc<sup>+</sup>/Fc couple (Figure 2). Addition of 1 eq. of NaOPiv shifted the oxidation to about 0.83 V. The oxidation of NaOPiv occurred only at potentials higher than 0.9 V. Thus, NaOPiv facilitated the oxidation of **1a**. We tentatively attributed this promotion to the formation of a substrate-base complex **6a**. A substrate without double bond (**1ae**) gave an oxidation peak at a similar potential, while adding -OMe to the phenyl of **1a** shifted the oxidation to 0.56 V (for **1g**). These results indicate that the initial oxidation gives a conjugated amidyl radical. Interestingly, when Cu(OAc)<sub>2</sub> (20 mol%) was added, the CV curve remained largely intact. This result shows that the trapping and transformation of radicals by the Cu catalyst have no obvious influence on the initial oxidation step. In the absence of **1a** but the presence of NaOPiv, the oxidation of Cu(I) to Cu(II) was observed at -0.40 V (Figure S1, Supporting Information), indicating a facile

process. No catalytic wave was observed when 1 eq. of **1a** was added (Figure S1), ruling out a Cu(II) catalyzed process for the cyclization reaction.



**Figure 2.** CVs of different reaction mixtures. The potential is versus Fc<sup>+/0</sup>/Fc. Concentration of reagents (if applicable): 0.01 M **1**, 0.01 M NaOPiv, 0.002 M Cu(OAc)<sub>2</sub>, 0.1 M NBu<sub>4</sub>BF<sub>4</sub> as electrolyte. Conditions: DCM+MeOH (1:1) as solvent, scan rate 100 mV/s.

Based on the above results, we propose the following mechanism for the electrochemical formal aza-Wacker cyclization (Figure 3). First, the substrate **1** associates with the base to give an adduct **6**, which is oxidized at the anode to give an amidyl radical **7**. The radical undergoes 5-exo-trig cyclization to afford the alkyl radical **8**, which is captured by Cu(II) to generate a formal Cu(III) alkyl intermediate.<sup>10a</sup> Subsequent elimination, probably assisted by the base, furnishes the alkene product **2** and yields a Cu(I) species. The latter is oxidized at the electrode to Cu(II) to re-enter the catalytic cycle.



**Figure 3.** Proposed reaction mechanism.

In summary, by integrating electrochemical oxidation with Cu catalysis, we have developed a formal aza-Wacker cyclization method. This tandem process enables the transformations of substrates that give rise to secondary and primary alkyl radical intermediates, broadening the reaction scope significantly beyond the previous limit. A wide range of 5-membered N-containing heterocycles bearing a pendant, functionalizable alkene moiety can be synthesized under mild conditions.

## Acknowledgements

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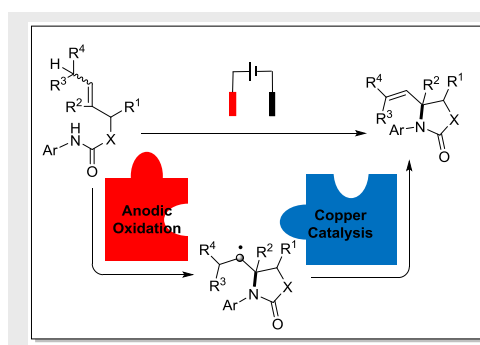
**Keywords:** Electrochemical organic synthesis, copper, radical reactions, aza-Wacker cyclization, alkene functionalization

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