Electrochemistry Hot Paper

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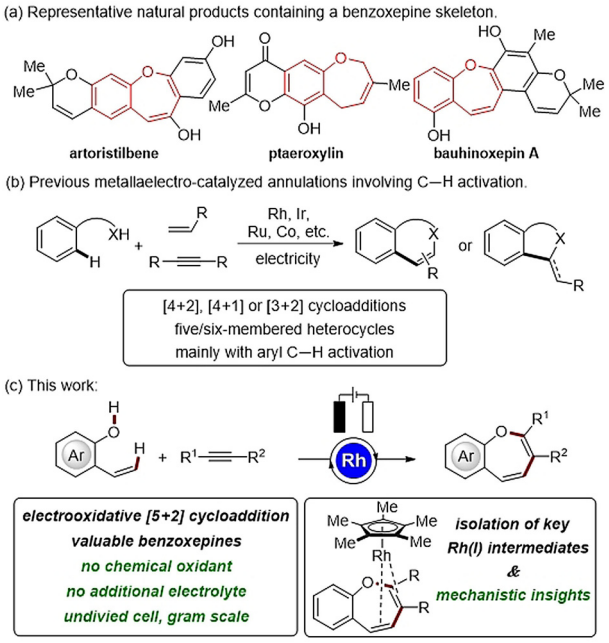
Electrooxidative Rhodium-Catalyzed [5+2] Annulations via C–H/O–H Activations

*Yulei Wang, João C. A. Oliveira, Zhipeng Lin, and Lutz Ackermann**

Abstract: *Electrooxidative annulations involving mild transition metal-catalyzed C–H activation have emerged as a transformative strategy for the rapid construction of five- and six-membered heterocycles. In contrast, we herein describe the first electrochemical metal-catalyzed [5+2] cycloadditions to assemble valuable seven-membered benzoxepine skeletons by C–H/O–H activation. The efficient alkyne annulation featured ample substrate scope, using electricity as the only oxidant. Mechanistic studies provided strong support for a rhodium(III/I) regime, involving a benzoxepine-coordinated rhodium(I) sandwich complex as the catalyst resting state, which was re-oxidized to rhodium(III) by anodic oxidation.*

Based on major achievements in the C–H activation arena during the past two decades, transition metal-catalyzed annulations involving the activation of otherwise unreactive C–H bonds have revolutionized the art of preparing cyclic compounds.[1–4] Despite indisputable advances, sacrificial chemical oxidants, such as $Cu(OAc)_2$ and AgOAc, are generally required to facilitate these processes, thus resulting in the generation of undesired byproducts and reducing the atom economy.

Electricity has been considered as a green and atom-economic redox equivalent.[5,6] Significant recent momentum has been gained by the merger of electrocatalysis with organometallic C–H activation.[7–11] These reactions have provided efficient routes for the assembly of a variety of heterocycles, normally five- and six-membered rings through formal [3+2][9] or [4+1][10] or [4+2][11] cycloadditions, respectively, with major contributions by the groups of Mei, Lei, Xu, and Ackermann, among others (Scheme 1 b). However, while seven-membered rings, such as benzoxepine derivatives, are the core structures of many natural products and pharmacologically relevant molecules (Scheme 1 a),[12] the construction of these scaffolds by means of metallaelectro-catalyzed annulations has proven elusive. Moreover, while rhodium catalysts have been widely used in C–H activation, the key low-valent rhodium(I) intermediates could seldom be isolated and their redox-chemistry was rarely studied by electroanalysis. Within our program on sustainable C–H activation,[13] we herein report on a uniquely efficient electrooxidative rhodium(III/I)-catalyzed annulation reaction to assemble the valuable seven-membered benzoxepine skeleton (Scheme 1 b). Salient features of our approach comprise a) the first electrooxidative [5+2] cycloaddition, b) annulations by resource economical O–H/C–H functionalization, c) electrons as catalysts in cathodic proton reduction, d) isolation of key rhodium(I) intermediates and e) detailed mechanistic insights into electrooxidative rhodium catalysis.



Scheme 1. Electrochemical metal-catalyzed C–H annulation.

We initiated our studies by exploring reaction conditions for the envisioned electrochemical [5+2] cycloadditions using 2-vinylphenol (**1a**) and diphenylacetylene (**2a**) in an undivided cell setup equipped with graphite felt (GF) and platinum plate (Pt) as anode and cathode material, respectively (Table 1). After considerable experimentations, the desired product **3aa** was isolated in 88% yield with $[Cp^*RhCl_2]_2$ (2.5 mol%), NaOPiv (2.0 equiv) as additive in *t*AmOH/H_2O (3:1) at 100 °C for 18 h (Table 1, entry 1). The [5+2] annulation was not viable in the absence of NaOPiv,[14] while KOAc in lieu of NaOPiv afforded a sharp decrease of

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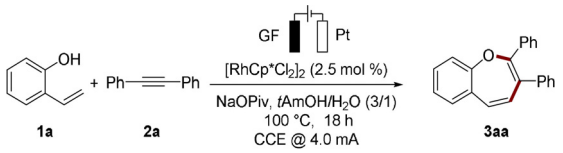
Table 1: Optimization of the rhodium-catalyzed [5+2] cycloadditions.[a]



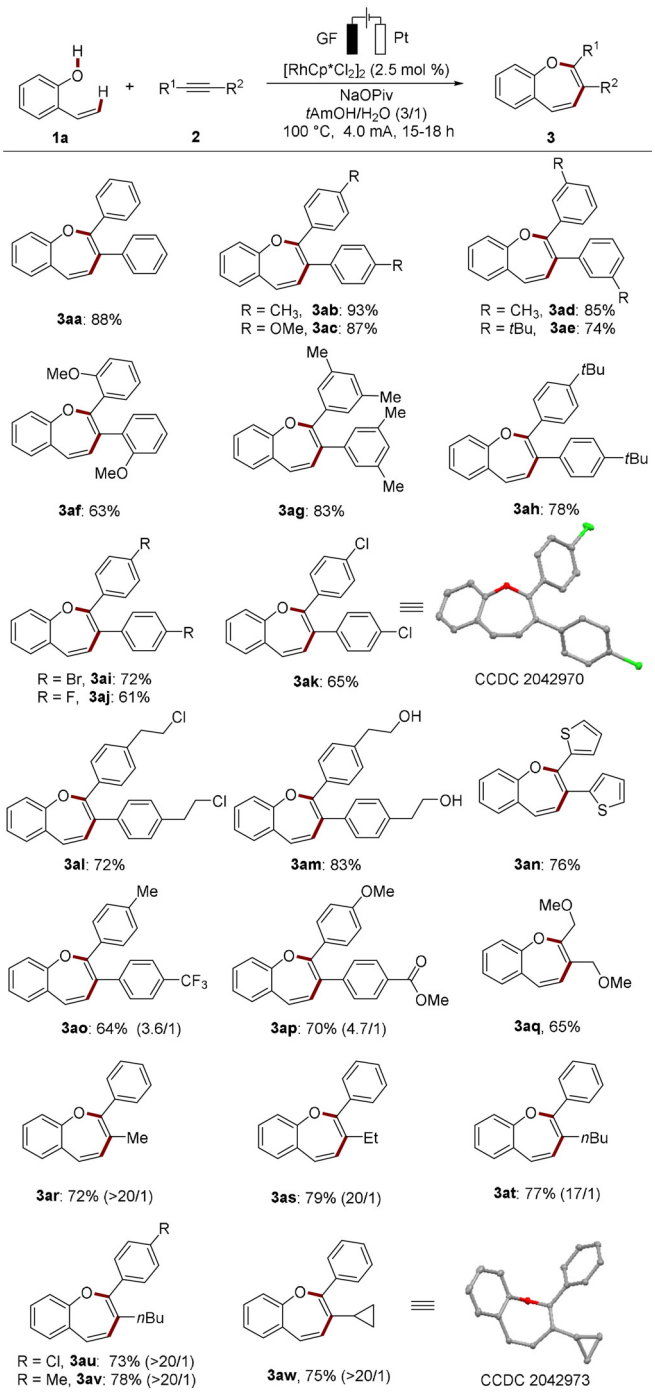
Entry	Variation from standard conditions	**3aa** [%][b]
1	no change	88
2	no NaOPiv	trace
3	KOAc in place of NaOPiv	44
4	H_2O	47
5	*t*AmOH	15
6	GF as cathode electrode	trace
7	8 mA, 9 h	65
8	no electricity	7
9	under N_2	79
10	$Pd(OAc)_2$ in place of $[Cp^*RhCl_2]_2$	0
11	$[Cp^*CoI_2]_2$ in place of $[Cp^*RhCl_2]_2$	0
12	$[Cp^*IrCl_2]_2$ in place of $[Cp^*RhCl_2]_2$	0

[a] Undivided cell, GF anode, Pt cathode, constant current = 4 mA, **1a** (1.0 mmol), **2a** (0.5 mmol), NaOPiv (1.0 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), solvent (4 mL), under air, 18 h. [b] Yields of isolated product **3aa**.

the yield (Table 1, entries 2–3). With H_2O or *t*AmOH alone as the solvent the electrocatalysis proved to be inefficient (Table 1, entries 4–5). Replacing the platinum cathode by a GF electrode inhibited the electrocatalysis (Table 1, entry 6). Increasing the current to 8 mA reduced the yield of product **3aa** to 65%, and a control experiment confirmed the essential role of the electricity for the electrooxidative annulation (Table 1, entries 7–9). Reactions with other transition-metal catalysts, including $Pd(OAc)_2$ as well as Cp*-ligated iridium and cobalt complexes, proved to be ineffective for the annulation process (Table 1, entries 10–12).

With the optimized reaction conditions for the electrochemical [5+2] cycloadditions in hand (Table 1, entry 1), its performance was first explored with a set of substituted alkynes **2** (Scheme 2). The annulation was amenable to diverse diaryl alkynes **2** featuring both electron-withdrawing as well as electron-donating substituents on the aryl group (**3ab**–**3an**). Functional groups, including chloro, bromo, and even alkyl chloride as well as unprotected primary alcohol, were well tolerated. The annulation with unsymmetrical diaryl alkynes **2o** and **2p** results in 3.6:1 and 4.7:1 regioselectivities, respectively. The rhodaelectro-catalysis was also effective for dialkyl alkyne **2q**. Notably, unsymmetrical arylalkyl alkynes **2r**–**2w** were also efficiently converted to the corresponding benzoxepines with high levels of regiocontrol placing the alkyl group distal to the heteroatom (**3ar**–**3aw**). This regioselectivity was assessed by means of computational studies at the PW6B95-D4/def2-QZVP + SMD (methanol)//PBE0-D3(BJ)/def2-SVP level of theory (Figure 1).[15] The regioisomer **3aw** was shown to be favored, placing the aryl group proximal to the heteroatom. Noncovalent secondary interactions play a dominant role in the stabilization of the preferred transition state.

The scope of the electrorhoda-catalyzed annulative reaction was examined with diversely substituted 2-vinylphenols



Scheme 2. Rhodaelectro-catalyzed [5+2] annulations with alkynes **2**.

1 (Scheme 3). Various phenols **1** were thereby selectively converted into the desired products **3** in high to excellent yields (**3ba**–**3ma**). Remarkably, the power of the metallaelectrocatalysis was embodied in the chemo-selective C–H functionalization/annulation with sensitive iodovinylphenol **1l** to afford the desired product (**3la**).

The fluorescent BODIPY motifs are widely used as effective biological labels, luminescent tags and laser dyes.[17] To our delight, the BODIPY-containing alkynes are suitable substrates for the metallaelectro-catalyzed annulations, and corresponding fluorescence-labeled benzoxepines (**3ax**–**3ay**)

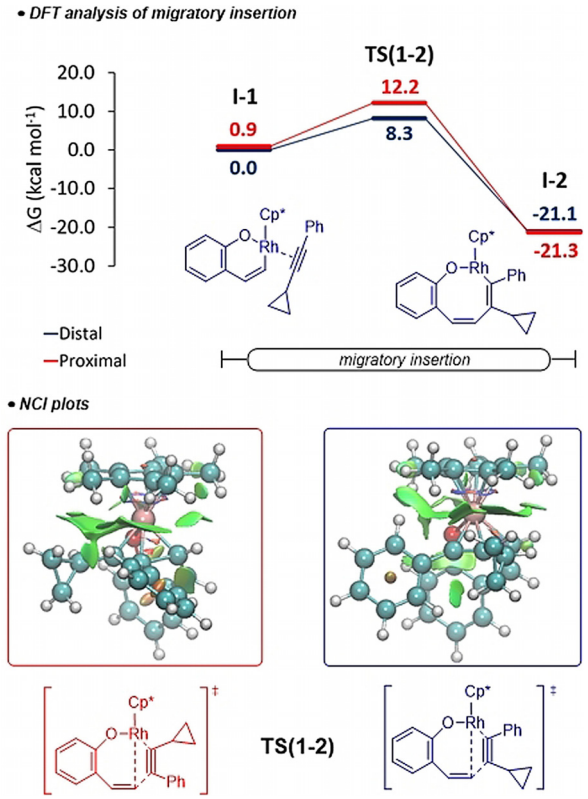
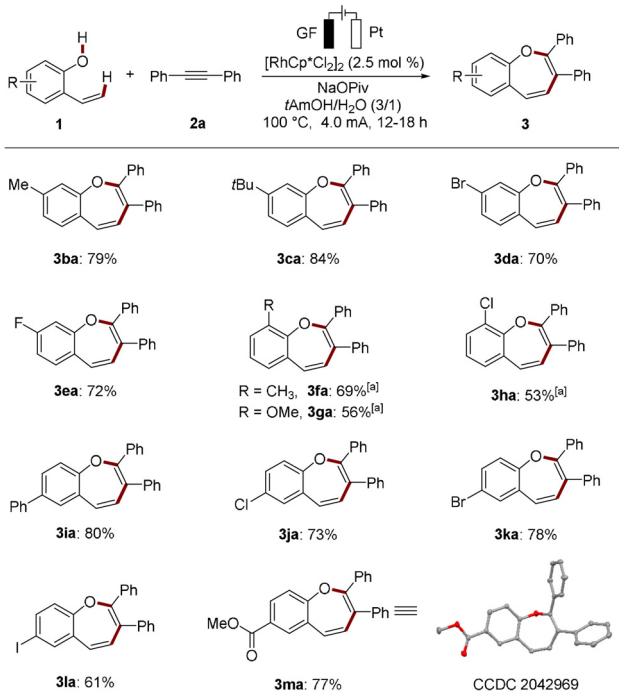
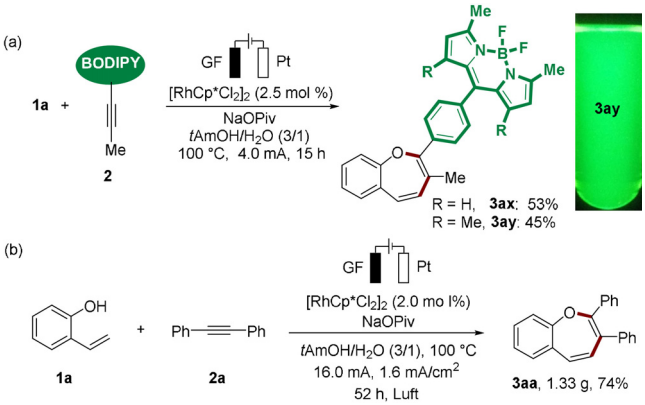


Figure 1. Computed Gibbs free energy profiles in kcal mol^{-1} for the regioselectivity of the migratory insertion step of alkyne **3w** calculated at the PW6B95-D4/def2-QZVP + SMD(methanol)//PBE0-D3(BJ)/def2-SVP level of theory and visualization of noncovalent interactions calculated from the NCI plot for the respective transition states. In the latter, strong attractive interactions are given in blue and weak attractive interactions are given in green, respectively, while red corresponds to strong repulsive interactions.



Scheme 3. Rhodaelectro-catalyzed [5+2] cycloadditions with 2-vinylphenols. [a] 5.0 mol % $[RhCp^*Cl_2]_2$.



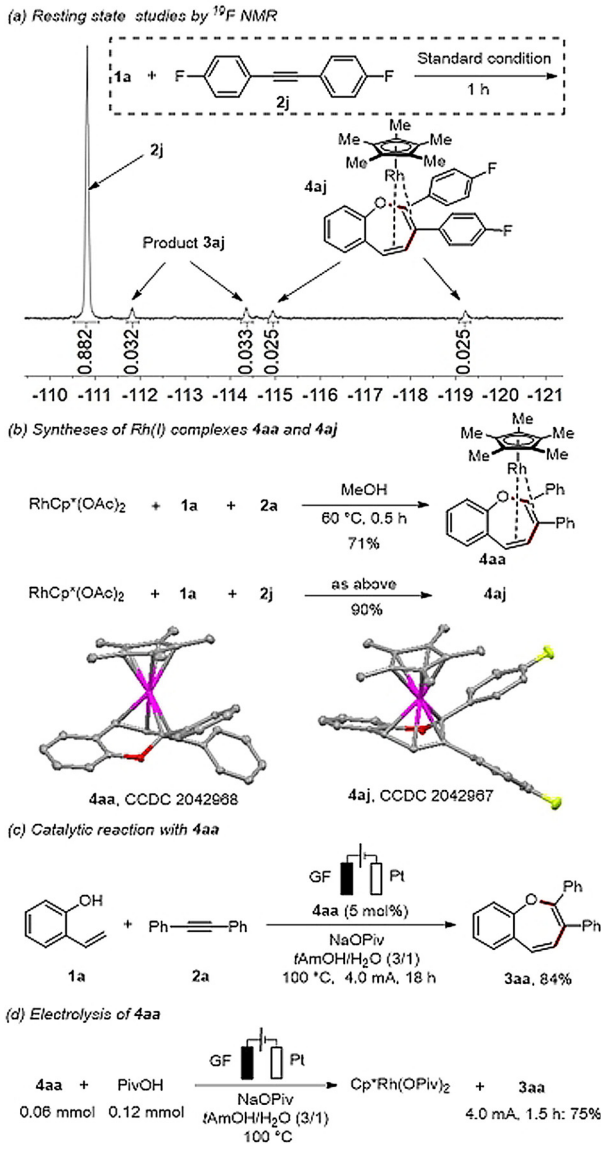
Scheme 4. a) Syntheses of BODIPY-labeled benzoxepines. b) Gram-scale synthesis of **3aa**.

could be easily obtained in one step (Scheme 4a). This transition metal-catalyzed C–H activation/annulation to assemble various BODIPY-labeled heterocycles would have great potential applications in drug deliveries, dyes, and optoelectronics.

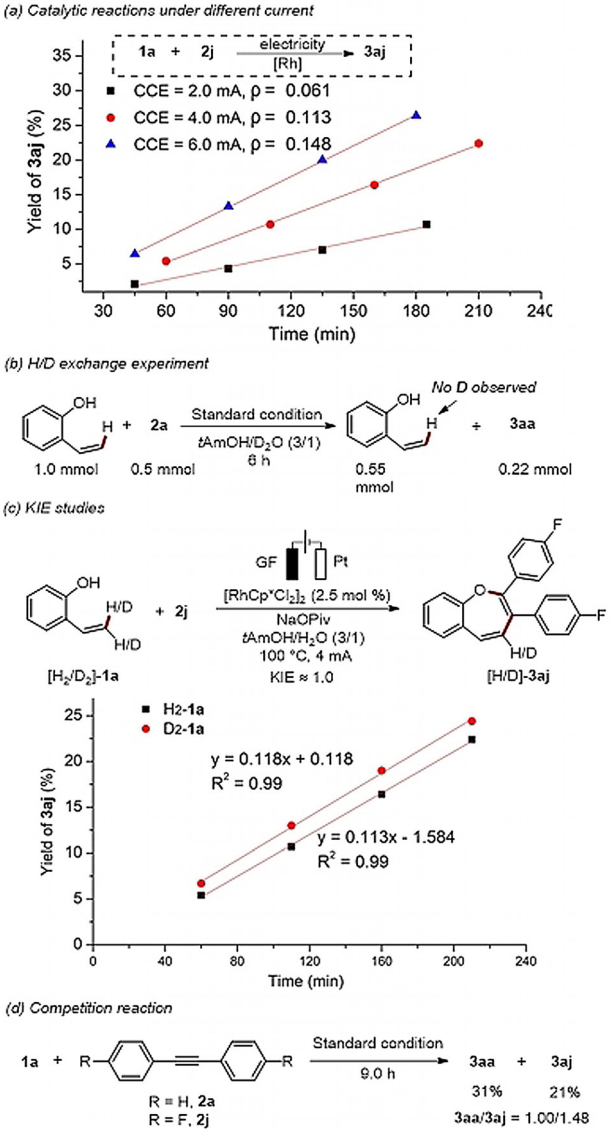
The scalability of the electrochemical rhodium-catalyzed [5+2] annulation was further demonstrated for the assembly of benzoxepines **3**. The gram-scale reaction of substrates **1a** and **2a** hence yielded 1.33 g of the desired product **3aa** (Scheme 4b).

To gain further insight into the reaction mechanism, we conducted a series of experiments. Monitoring the catalytic process by NMR spectroscopy revealed that a low-valent rhodium complex **4** was likely the catalyst resting state in the electrorhoda-catalyzed annulative reaction (Scheme 5a). Notably, the corresponding rhodium(I) complexes **4aa** and **4aj** could be prepared and isolated by the reaction of $Cp^*Rh(OAc)_2$ with the substrates **1a** and **2a** or **2j**, respectively. X-ray diffraction analysis featured rhodium(I) sandwich complexes in which the benzoxepines **3** are coordinated to the metal center as four-electron ligands (Scheme 5b).[16] Complex **4aa** proved to be competent in the catalytic reaction (Scheme 5c). Electrolysis of **4aa** released product **3aa**, and the rhodium(I) was oxidized to the rhodium(III) species $Cp^*Rh(OPiv)_2$ (Scheme 5d). Increasing the electric current resulted in a higher initial reaction rate, indicating the reoxidation of rhodium(I) to rhodium(III) to be the rate-determining step (RDS) (Scheme 6a). H/D exchange experiments were conducted using D_2O as the deuterium source, and deuterium incorporation was not observed in the recovered 2-vinylphenols **1a** (Scheme 6b). Kinetic studies suggested a facial vinylic C–H metalation with a KIE value of $k_H/k_D \approx 1.0$ (Scheme 6c). Competition experiments with alkynes **2a** and **2j** revealed the greater reactivity of the electron-deficient alkyne **2j** (Scheme 6d).

CV studies of rhodium(I) complexes **4aa** and **4aj** exhibited irreversible oxidation waves at −0.058 V versus $Fc^{0/+}$ and −0.029 V versus $Fc^{0/+}$, respectively (Figure 2). It is reasonable that the latter has a higher oxidation potential



Scheme 5. Isolation and electrolysis studies of rhodium(I) intermediates.



Scheme 6. Summary of key mechanistic findings.

since **4aj** possesses a electron-deficient metal center compared to **4aa**. A constant potential was conducted at 1.0 V affording the desired product **3aa** in 61% yield. Additional CV studies showed that the rhodium(I) intermediates **4aa** and **4aj** had lower oxidation potential than the substrates and products (Figure S10). The addition of PivOH had no significant influence on the oxidation potential of complex **4aa** (Figure S11).

On the basis of our findings, a plausible catalytic cycle is presented that commences with a facile O–H/C–H activation to afford a rhodacycle **A** (Figure 3). Then, alkyne coordination–insertion occurs to produce intermediate **C**, which rapidly undergoes reductive elimination to deliver the rhodium(I) sandwich complex **4**. Finally, the rhodium(I) species is re-oxidized to rhodium(III) at the anode, releasing the desired product **3** and generating molecular hydrogen as the by-product at the cathode. An alternative oxidation-

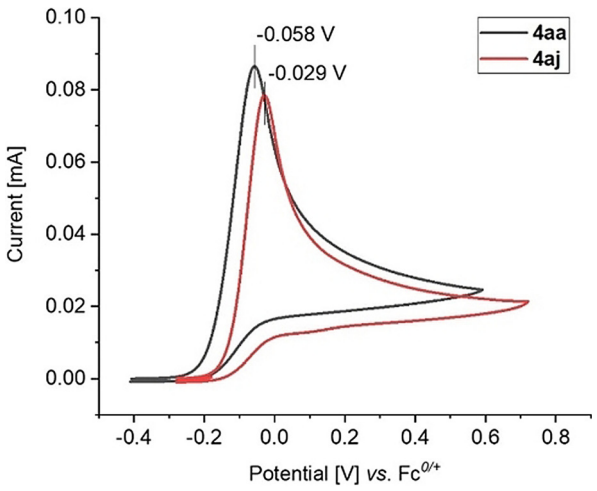


Figure 2. Cyclic voltammetry studies. Conditions: **4aa** (2.5 mM) or **4aj** (2.5 mM), nBu$_4$NPF$_6$ (0.1 M), MeCN, 100 mVs^{-1}.

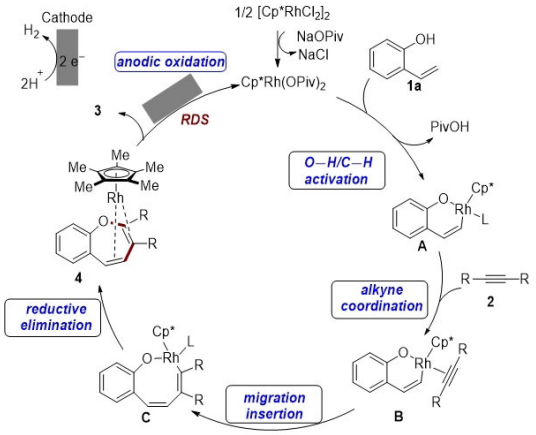


Figure 3. Proposed catalytic cycle.

induced reduction elimination pathway may also be viable as depicted in Figure S9.[15]

In conclusion, we have reported on the first electrocatalyzed [5+2] annulations to assemble valuable seven-membered benzoxepine skeletons by C–H/O–H activation. The versatility of the rhodaelectrosynthesis was demonstrated by its broad substrate scope and excellent functional group tolerance. The C–H activation employed electrons as catalysts for cathodic proton reduction, generating hydrogen as the sole byproduct. Detailed mechanistic studies provided strong support for a fast C–H rhodation and a rhodium(III/I) regime involving an efficient electrooxidation of the key benzoxepine-ligated rhodium(I) intermediate.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: [5+2] cycloaddition · benzoxepine · C–H activation · electrochemistry · electrooxidative annulation

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[15] For detailed information, see the Supporting Information.

[16] Deposition numbers 2042970 (**3ak**), 2042973 (**3as**), 2012969 (**3ka**), 2042968 (**4aa**) and 2042967 (**4aj**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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