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Electrocatalysis

Ruthenaelectro-Catalyzed Domino Three-Component Alkyne Annulation for Expedient Isoquinoline Assembly

*Xuefeng Tan, Xiaoyan Hou, Torben Rogge, and Lutz Ackermann**

Dedicated to Professor Paul Knochel on the occasion of his 65th birthday

Abstract: *The electrochemical three-component assembly of isoquinolines has been accomplished by ruthenaelectro-catalyzed C–H/N–H functionalization. The robustness of the electrocatalysis was reflected by an ample substrate scope, an efficient electrooxidation, and an operationally friendly procedure. The isolation of key intermediates and detailed mechanistic studies, including unprecedented cyclovoltammetric analysis of a seven-membered ruthenacycle, provided support for an unusual ruthenium(II/III/I) regime.*

Transition metal-catalyzed C–H activation has been recognized as an increasingly viable transformative platform in molecular syntheses.[1] Nitrogen-containing heterocycles are omnipresent in bioactive molecules of interest to medicinal chemistry and pharmaceutical industries.[2] Particularly, isoquinolines feature diverse activities, such as cardiovascular,[3] anti-tumor,[4] anti-inflammatory,[5] or anti-malaria[6] properties. Transition metal-catalyzed imino group-directed C–H activation, along with a subsequent annulation of alkynes represents one of the most efficient strategies to construct isoquinolines.[7,8] In the past decade, considerable efforts have thus been devoted to the development of oxidative C–H activations. These largely required stoichiometric amounts of chemical oxidants, such as copper or silver salts.[7,9] In addition, the imines largely needed to be isolated prior to catalysis.[9]

In recent years, the use of electricity as a formal redox reagent has been recognized as an increasingly viable, environmentally friendly strategy to empower chemical reactions.[10] Significant recent impetus was gained by the merger of electrocatalysis with oxidative C–H activation, thus avoiding the use of often toxic metal oxidants.[11] Compared with rhodium[12] and iridium[13] electrocatalysis, economically attractive ruthenaelectrocatalysis continues to be underdeveloped.[14] Within our program on electrochemical C–H activation,[15] we have now devised a sustainable ruthenaelectro-catalyzed three-component reaction to assemble versatile isoquinolines in a domino manner.[16] Salient features of our findings include 1) multi-component assembly in a one-pot fashion with a cost-effective ruthenium catalyst,[8f] 2) isolation and full characterization of ruthenacycle intermediates, and 3) mechanistic insights into oxidation-induced reductive elimination[17] at ruthenium(II) by experiments and calculation (Figure 1)

At the outset of our studies, various reaction conditions were explored for the envisioned ruthenium-catalyzed electrooxidative three-component annulation of acetophenone **1a**, alkyne **2a**, and NH_4OAc in an operationally simple undivided cell setup equipped with a graphite felt (GF) anode and a platinum cathode (Table 1 and Table S1 in the Supporting Information). $[Ru(OAc)_2(p\text{-cymene})]$ was found to be superior as compared to $[RuCl_2(p\text{-cymene})]_2$, even without additives (Table 1, Entries 1–3). An increased reaction temperature proved beneficial (Table 1, Entries 3–5). An evaluation of various solvents (Table S1) showed that alcoholic solvents enabled a higher efficacy than aprotic solvents, while the acidic trifluoroethanol (TFE) was proven best. These findings can be rationalized in terms of a facile condensation and stabilization of the imine through hydrogen bonding. The optimal current was found to be 2.5 mA (Table 1, Entry 6). A variation in the stoichiometry of NH_4OAc did not show any significant difference (Table 1, Entries 6 and 7). Increasing the amount of alkyne **2a** and changing the cathode material to nickel foam yielded **3aa** in a slightly improved efficiency (Table 1, Entries 8 and 9).

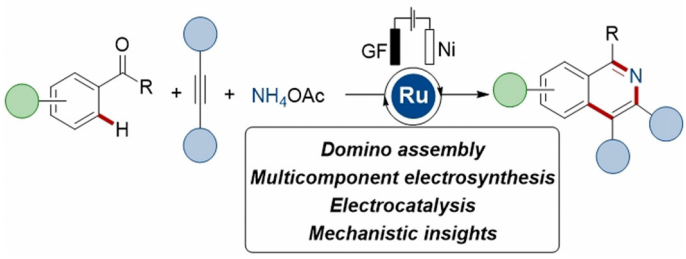

Figure 1. Ruthenium-catalyzed electrochemical three-component synthesis of isoquinoline.

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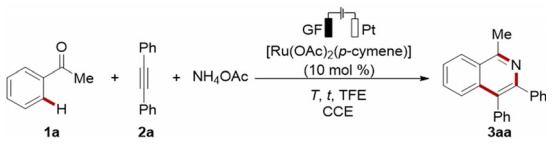
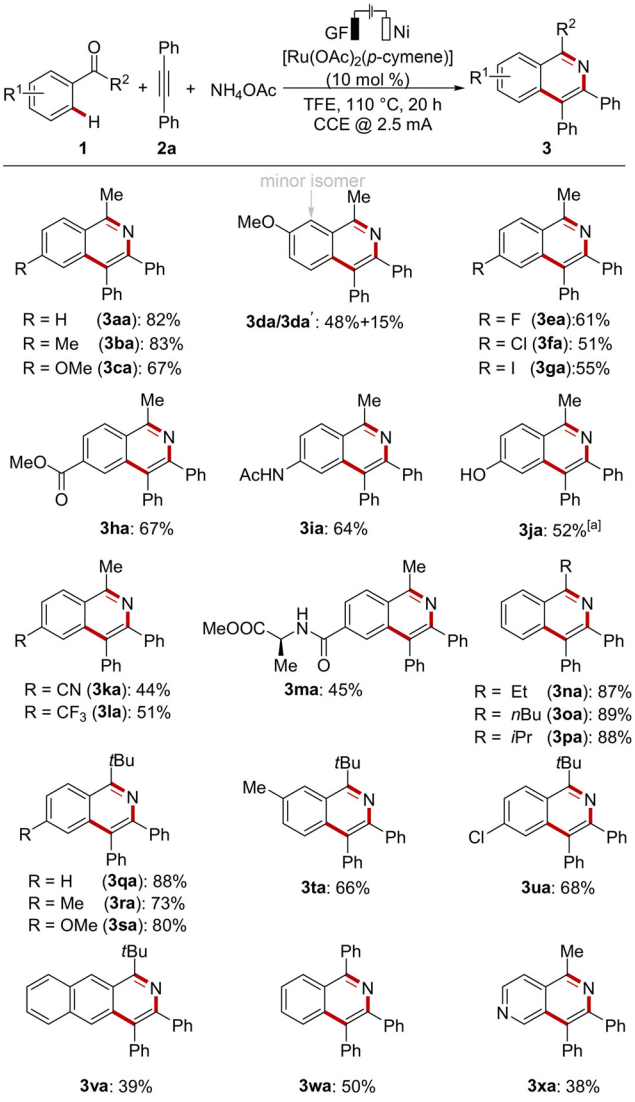
Table 1: Optimization of the ruthenium-catalyzed three-component annulation.[a]



Entry	Current [mA]	*t* [h]	*T* [°C]	Yield [%]
1	4	14	95	22[b]
2	4	14	95	33[b,c]
3	4	14	95	33
4	4	14	80	19
5	4	14	110	47
6	2.5	20	110	50
7	2.5	20	110	50[d]
8	2.5	20	110	55[e]
9	2.5	20	110	63[e,f]
10	2.5	20	110	72[e,f,g]
11	2.5	20	110	82[e,f,g,h]
12	1.2	36	110	65[e,f,g,h,i]
13	–	20	110	12[j]
14	–	20	110	19[k]
15	–	20	110	NR[l]

[a] **1a** (0.3 mmol), **2a** (0.45 mmol), $[Ru(OAc)_2(p\text{-cymene})]$ (10 mol%), NH_4OAc (4.0 equiv), trifluoroethanol (3.5 mL), graphite felt anode (GF) ($10\times10\times6$ mm^3), platinum plate cathode ($10\times15\times0.25$ mm^3), under N_2 in a 10 mL vessel. [b] $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) instead of $[Ru(OAc)_2(p\text{-cymene})]$. [c] KPF_6 (20 mol%) added. [d] NH_4OAc (2.0 equiv). [e] **2a** (0.6 mmol). [f] Nickel foam as cathode. [g] In a 25 mL vessel. [h] Vessel equipped with an oil bubbler. [i] $[Ru(OAc)_2(p\text{-cymene})]$ (5 mol%). [j] Under air. [k] Under oxygen (O_2 balloon). [l] $Cu(OAc)_2$ (2 equiv).



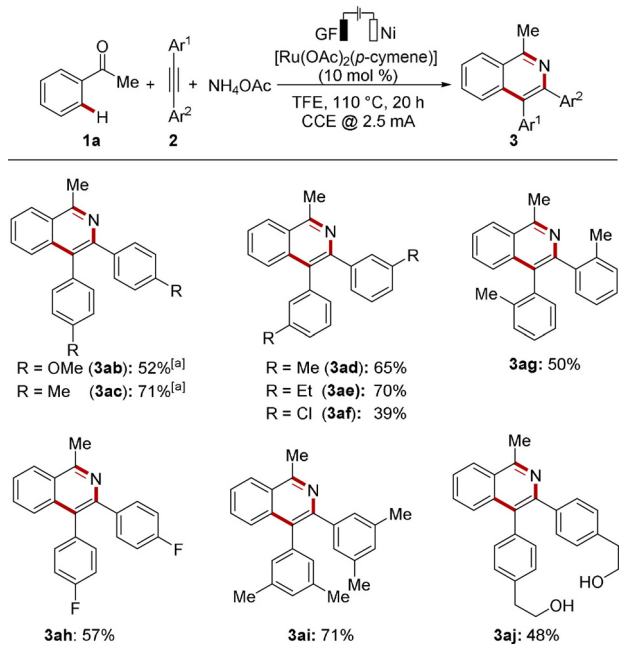
Scheme 1. Ruthena-domino-electrocatalysis with ketones **1**. [a] Starting material is 4-acetoxyl acetophenone.

Careful GC–MS analysis revealed that the alkyne was fully consumed after the reaction when nickel foam was used as the cathode material, generating the corresponding *E*/*Z*-alkenes through hydrogenation with molecular H_2 formed at the cathode by paired electrolysis. Therefore, we employed a larger reaction flask, facilitating the H_2 dispersion into the expanded volume (Table 1, Entry 10). Further, we employed an oil bubbler, which allowed for the H_2 release, benefiting the chemoselectivity for product **3aa** formation (Table 1, Entries 11, 12, and the SI). With air, oxygen or with $Cu(OAc)_2$ as the oxidant, unsatisfactory results were obtained, reflecting the unique efficacy of the electrocatalysis (Table 1, Entries 13–15).

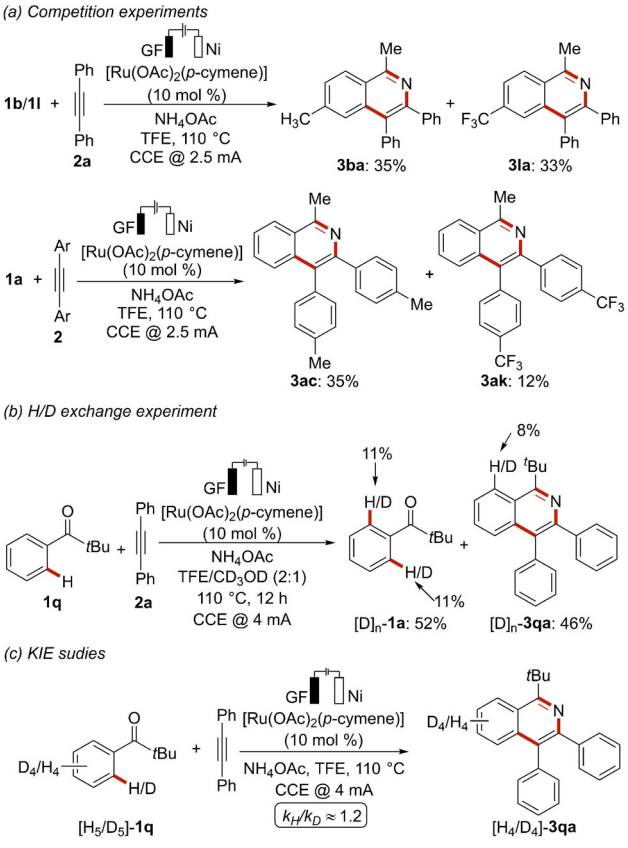
With the optimized reaction conditions in hand, we next examined the viable substrate scope of the ruthenaelectro-catalyzed three-component annulation with diverse ketones **1** (Scheme 1). Electron-rich as well as electron-deficient aromatic ketones **1a**–**1x** were amenable to the ruthenaelectro-catalyzed domino multi-component synthesis of isoquinolines **3**. Notably, a diverse array of valuable functional groups, including halogens (**3ea**–**3ga**), ester (**3ha**), amide (**3ia**), acetoxyl (**3ja**), and cyano (**3ka**) groups, were tolerated under the electrochemical conditions, highlighting a notable potential for further late-stage diversification. The amino ester-containing product **3ma** indicated the power for the synthesis of bio-fluorescent probes. The site-selectivity for *meta*-substituted ketones **1t** and **1v** was governed by steric hindrance, while *meta*-methoxy-substituted acetophenone **1d** delivered the less congested product **3da** preferentially.

We then turned our attention to different alkynes **2** for the ruthenaelectro-catalyzed three-component annulation (Scheme 2). Electron-rich or electron-deficient alkynes **2** efficiently delivered the desired products **3**, while electron-rich alkynes exhibited a slightly higher innate reactivity. Due to the poor solubility of *para*-substituted alkynes **2b** and **2c** in TFE, we employed a solvent mixture consisting of TFE and toluene. The alcohol-containing product **3aj** should prove valuable for late-stage derivatization.

Intrigued by the versatility of the ruthenaelectro-catalyzed three-component annulation, we became interested in delineating the catalyst's mode of action. Competition experiments revealed that the substitution pattern on the ketone **1** did not have a significant influence on the reactivity, whereas electron-donating substituents on the alkynes **2** resulted in a higher reactivity than electron-withdrawing substituents (Scheme 3a). Reactions conducted with deuter-



Scheme 2. Ruthena-domino-electrocatalysis with alkynes **2**. [a] Toluene/TFE = 6:1.



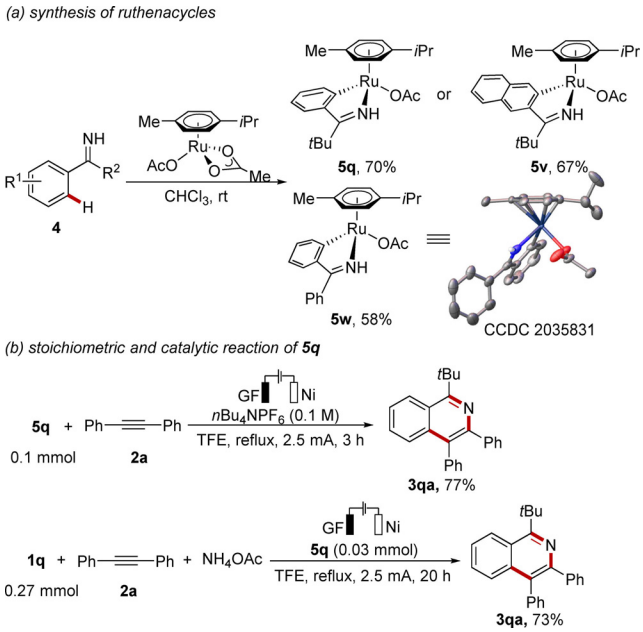
Scheme 3. Summary of key mechanistic experiments.

ated methanol as a co-solvent revealed the reversibility of a fast C–H activation step (Scheme 3b). In good agreement with this finding, kinetic studies provided strong support for a fast C–H metalation with a minor kinetic isotope effect (KIE) of $k_H/k_D \approx 1.2$ (Scheme 3c).

Next, we intended the isolation of key intermediates. Three ruthenacycle complexes **5q**, **5v**, and **5w** were thereby isolated and complex **5w** was unambiguously characterized by X-ray diffraction analysis (Scheme 4a). It is noteworthy that the ^{1}H NMR resonances of the ruthenacycle complexes in [D_4]-MeOH were split into two sets of resonances in contrast to the ^{1}H NMR in $CDCl_3$, which showed only one set of resonances.[18] This is likely caused by an equilibrium of the ruthenacycles and the OAc disassociation from the metal center, which facilitates the alkyne coordination to the ruthenium. Notably, the metallacycle **5q** was found to be competent under stoichiometric and catalytic reaction conditions (Scheme 4b).

To gain insights into the catalyst's working mode, we performed density functional theory (DFT) studies at the ωB97X-V/def2-QZVP + SMD(TFE)//TPSS-D3(BJ)/def2-TZVP level of theory.[18] Initial one-electron oxidation of seven-membered ruthenacycle **A** with an oxidation potential of 0.7 V versus $Fc^{0/+}$ takes place and leads to the formation of ruthenium(III) complex $\mathbf{A}^+$ (Figure 2). Afterwards, reductive elimination occurs to generate $\mathbf{B}^+$, which subsequently undergoes a second one-electron oxidation to ruthenium(II) with a calculated oxidation potential of 0.5 V. Finally, facile deprotonation and decoordination of acetic acid takes place to deliver the 18-electron ruthenium sandwich-type complex $\mathbf{D}^{2+}$.

Inspired by the DFT calculations, we intended to isolate the key intermediate of the reaction of ruthenacycle **5** with alkyne **2**. We were pleased to obtain the seven-membered ring intermediate **6** through a stoichiometric reaction of ruthenacycle **5v** with alkyne **2a**, and ruthena(II)cycle **6** was unambiguously characterized by X-ray diffraction analysis (Sche-



Scheme 4. Study on C–H activation ruthenacycle complexes and X-ray analysis of **5w**.[19]

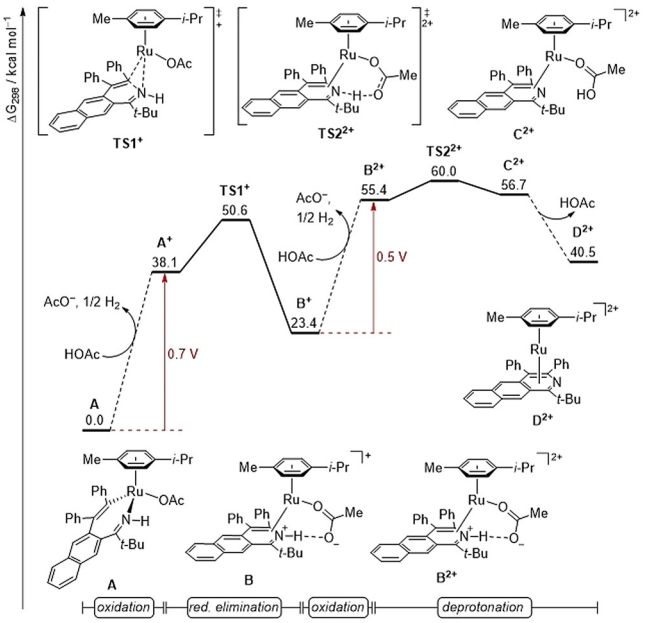
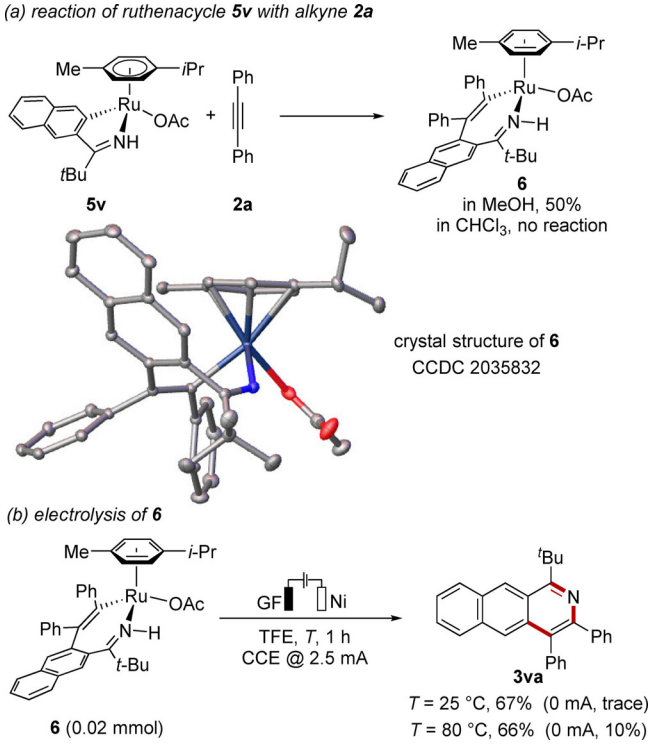


Figure 2. Relative Gibbs free energy profile in kcal mol^{-1} at the ωB97X-V/def2-QZVP + SMD(TFE)//TPSS-D3(BJ)/def2-TZVP level of theory. The given potential (red) corresponds to the half-wave potential versus $Fc^{0/+}$.

me 5a). Direct electrolysis of intermediate **6** in TFE delivered the desired isoquinoline product **3va**, irrespective of the reaction temperature (Scheme 5b).

Furthermore, we probed the electrochemical C–H activation by means of cyclovoltammetric analysis (Figure 3). At ambient temperature in TFE, substrates **1v** and **2a** as well as



Scheme 5. Isolation of key intermediate ruthenacycle **6**.[19]

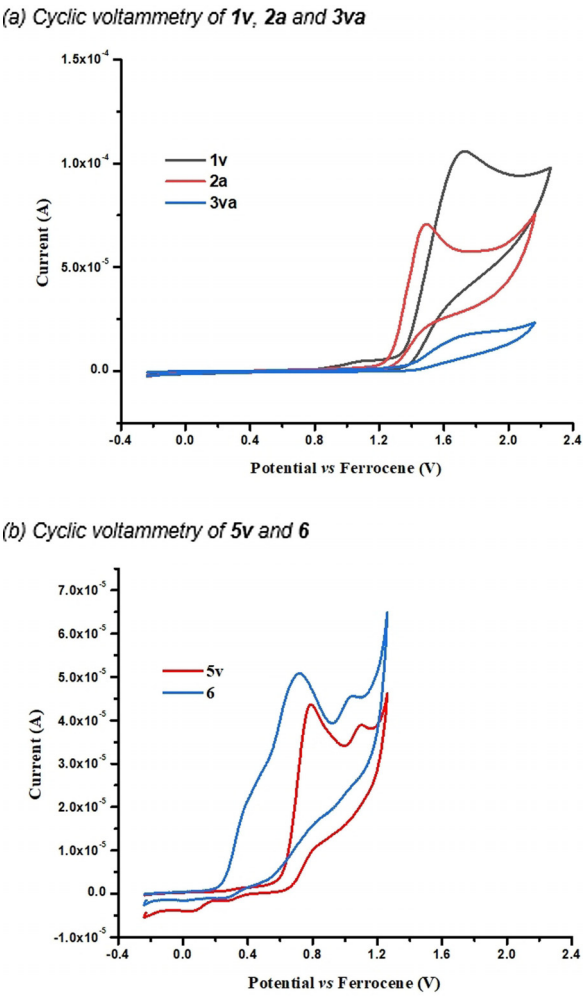


Figure 3. Cyclic voltammetry measurements in TFE under N_2 with 0.1 M nBu_4NBF_4 at room temperature with 100 mV s^{-1}.

product **3va** showed onset potentials of $E_{onset} > 1.2$ V versus ferrocene. In contrast, two irreversible oxidation events were observed for the C–H activated ruthenacycle **5v** with an onset potential of $E_{onset} = 0.60$ V versus ferrocene (Figure 3b). The seven-membered ruthenacycle **6** showed a significantly lower oxidation potential, with an onset potential of $E_{onset} = 0.20$ V versus ferrocene. Since the direct electrolysis of **6** efficiently delivered the desired product **3va** (Scheme 5b), these findings are supportive of an oxidation-induced reductive elimination within a ruthenium(II/III) regime. Alternatively, ruthenium (II/IV) or ruthenium (II/0) pathways appear less likely to be operative.[18]

Based on these detailed mechanistic studies, we propose the catalytic cycle to commence by in situ generation of the imine **4** and a fast organometallic C–H activation (Figure 4). Thereby, ruthena(II)cycle **5** is generated. Thereafter, migratory insertion occurs to furnish intermediate **6**. Then, anodic oxidation-induced reductive elimination by a ruthenium(II/III/I) manifold generates intermediate **9**. Further anodic oxidation and deprotonation of intermediate **9** generates intermediate **10**, which delivers the final product through ligand exchange, thus regenerating the ruthenium(II) catalyst.

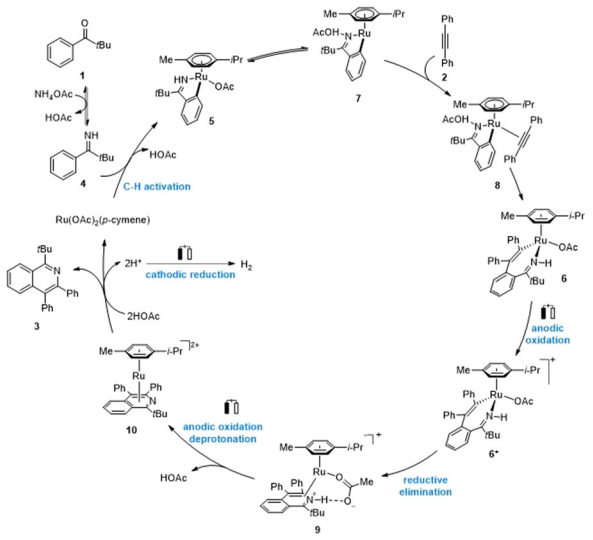


Figure 4. Proposed catalytic cycle.

In conclusion, we have reported on the unprecedented three-component electrochemical domino assembly of isoquinolines with electricity as the sole oxidant, generating only H_2 as byproduct. Well-defined ruthenacycles of C–H activation and a seven-membered ring intermediate were isolated and fully characterized by X-ray diffraction analysis, DFT calculations, and cyclovoltammetric analysis, providing strong support for a fast C–H activation and a ruthenium(II/III) manifold.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: annulation · C–H activation · domino reactions · electrocatalysis · ruthenium

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

[19] Deposition numbers 2035831 (**5w**) and 2035832 (**6**) 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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