

A Journal of the Gesellschaft Deutscher Chemiker A Deutscher Chemiker GDCh International Edition www.angewandte.org

Accepted Article

Title: Ruthenaelectro-Catalyzed Domino Three-Component Alkyne Annulation Expedient Isoquinoline Assembly

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Angew. Chem. Int. Ed. 10.1002/anie.202014289

Link to VoR: https://doi.org/10.1002/anie.202014289

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

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Dedicated to Prof. Dr. Paul Knochel on the occasion of his 65th birthday

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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 substrates 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] antiinflammatory^[5] or anti-malaria^[6] properties. Transition metalcatalyzed 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] iridium^[13] electrocatalysis, and economically-attractive ruthenaelectrocatalysis continues to be underdeveloped.[14] Within our program on electrochemical C-H activation,^[15] we have now devised a sustainable ruthenaelectro-catalvzed threecomponent 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 costruthenium catalvst.^[8f] effective 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. Ruthenium-catalyzed electrochemical three-component synthesis of isoquinoline.

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 NH₄OAc 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-cymene) was found to be superior as compared to [RuCl₂(*p*-cymene)]₂, even without additives (Table 1, Entries 1-3). An increased reaction temperature proved beneficial (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 as 2.5 mA (Entry 6). A variation in the stoichiometry of NH₄OAc did not show any significant difference (Entries 6-7). Increasing the amount of alkyne 2a and changing the cathode material to nickel foam yielded 3aa in a slightly improved efficiency (Entries 8-9). 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 H₂ formed at the cathode by paired electrolysis. Therefore, we employed a larger reaction flask, facilitating the H₂ dispersion into the expanded volume (Entry 10). Further, we employed an oil bubbler,

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which allowed for the H₂ release, benefiting the chemo-selectivity for product **3aa** formation (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 (Entries 13-15). *meta*-substituted ketones 1t and 1v was governed by steric hindrance, while *meta*-methoxy-substituted acetophenone 1d delivered the less congested product 3da preferentially.

 Table 1. Optimization of the ruthenium-catalyzed three-component annulation.

 [a]

Me +	Ph - + NH, Ph 2a	G [Ru(OA 40Ac	$F \blacksquare Pt$ $IO mol \%)$ T, t, TFE CCE	$\xrightarrow{\text{Me}}_{\text{Ph}} \xrightarrow{\text{Ne}}_{\text{Ph}} \xrightarrow{\text{Ne}}_{\text{Ph}}$
Entry	Current	<i>t</i> (h)	T(°C)	Yield (%)
1	4 mA	14	95	22 ^[b]
2	4 mA	14	95	33 ^[b,c]
3	4 mA	14	95	33
4	4 mA	14	80	19
5	4 mA	14	110	47
6	2.5 mA	20	110	50
7	2.5 mA	20	110	50 ^[d]
8	2.5 mA	20	110	55 ^[e]
9	2.5 mA	20	110	63 ^[e,f]
10	2.5 mA	20	110	72 ^[e,f,g]
11	2.5 mA	20	110	82 ^[e,f,g,h]
12	1.2 mA	36	110	65 ^[e,f,g,h,i]
13		20	110	12[]]
14		20	110	19 ^[k]
15		20	110	



[a] **1a** (0.3 mmol), **2a** (0.45 mmol), [Ru(OAc)₂(*p*-cymene)] (10 mol %), NH₄OAc (4.0 equiv.), trifluoroethanol (3.5 mL), graphite felt anode (GF) (10 x 10 x 6 mm³), platinum plate cathode (10 x 15 x 0.25 mm³), under N₂ in a 10 mL vessel. [b] [RuCl₂(*p*-cymene)]₂ (5 mol %) instead of [Ru(OAc)₂(*p*-cymene)]. [o] KPF₆ (20 mol %) added. [d] NH₄OAc (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*-cymene)] (5 mol %). [j] Under air. [k] Under oxygen (O₂ balloon). [I] Cu(OAc)₂ (2 equiv.).

With the optimized reaction conditions in hand, we next examined the viable substrate scope of the ruthenaelectrocatalyzed 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 Scheme 1. Ruthena-domino-electrocatalysis with ketones 1. [a] Starting material is 4-acetoxyl acetophenone.

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 here a solvent mixture consisting of TFE and toluene. The alcohol-containing product 3aj should prove valuable for late-stage derivatization.

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

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 deuterated 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 $k_{\rm H}/k_{\rm D} \approx 1.2$ (Scheme 3c).



Scheme 3. Summary of key mechanistic experiments.

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 ¹H NMR resonances of the ruthenacycle complexes in methanol- d_4 were split into two sets of resonances in contrast to the ¹H NMR in CDCl₃, 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).

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(a) synthesis of ruthenacycles



Scheme 4. Study on C–H activation ruthenacycle complexs and X-ray analysis of $5w.^{\rm [19]}$

To gain insights into the catalyst's working mode, we performed density functional theory (DFT) studies at the ω B97X-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 **A**⁺ (Figure 2). Afterwards, reductive elimination occurs to generate **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 **D**²⁺.



Figure 2. Relative Gibbs free energy profile in kcal mol⁻¹ at the ω B97X-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/+}.

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

(a) reaction of ruthenacycle 5v with alkyne 2a



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

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 product **3va** showed onset potentials of $E_{onset} > 1.2V$ 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 oxidationinduced reductive elimination within a ruthenium(II/III) regime. Alternatively, ruthenium (II/IV) or ruthenium (II/0) pathways appear less likely to be operative.^[18]

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(a) Cyclic voltammetry of 1v, 2a and 3va



(b) Cyclic voltammetry of 5v and 6



Figure 3. Cyclic voltammetry measurements in TFE under N_2 with 0.1 M $\mathit{n}\text{Bu4}\text{NBF}_4$ at RT with 100 mVs^1.

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 ruthenium(II) catalyst.





Figure 4. Proposed catalytic cycle.

In conclusion, we have reported on the unprecedented threecomponent 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.

Acknowledgements

Generous support by the DFG (Gottfried-Wilhelm-Leibniz award to L.A.) is gratefully acknowledged. We thank Dr. Christopher Golz (Göttingen University) for assistance with the X-ray diffraction analysis.

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

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- [18] For detailed information, see the Supporting Information.
- [19] CCDC 2035831 (**5w**) and 2035832 (**6**) contain the supplementary crystallographic data for this paper. These data can beobtained free of charge from Cambridge Crystallographic Data Centre.

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Entry for the Table of Contents



Ruthenium-catalyzed electrooxidative three-component syntheses of isoquinolines proved viable with ample scope. The isolation of key intermediates, along with DFT calculations revealed an unusual ruthenium(II/III/I) catalytic cycle.

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