A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202000762
Angew. Chem. 10.1002/ange.202000762

Link to VoR: http://dx.doi.org/10.1002/anie.202000762
http://dx.doi.org/10.1002/ange.202000762

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Aza-Ruthena(II)-Bicyclo-[3.2.0]-Heptadiene: Key Intermediate for Ruthenaelectro(II/III/I)-Catalyzed Alkyne Annulations

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Dedication

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Abstract: *A ruthenium-catalyzed electrochemical dehydrogenative annulation reaction of imidazoles with alkynes has been established, enabling the preparation of various bridgehead N−fused [5,6]-bicyclic heteroarenes through regioselective electrochemical C−H/N−H annulation without chemical metal oxidants. Novel aza-ruthena-bicyclo-[3.2.0]-heptadienes were fully characterized and identified as key intermediates. Mechanistic studies are suggestive of an oxidatively-induced reductive elimination pathway within a ruthenium(II/III) regime.*

Introduction

Transition metal-catalyzed C–H activations have emerged as a transformative platform,[1] with enabling applications to drug design,[2] natural product synthesis,[3] and material sciences.[4] As a consequence, a plethora of transition metal-catalyzed C–H/Het–H activation/alkyne annulations has emerged as a useful tool for the preparation of heterocycles.[5] However, these methods generally require a stoichiometric amount of organic or metal-based oxidant, such as toxic and/or expensive copper(II) or silver(I) salts. In recent years, the use of electricity as a formal redox agent to empower chemical reactions has been recognized as an increasingly viable, environmentally-friendly strategy.[6] Significant recent impetus was gained by the merger of electrocatalysis with oxidative C–H activation, thus avoiding the use of toxic and expensive metal oxidants.[7]

Despite considerable progress,[8] the development of new catalytic manifolds is hampered by a lack of mechanistic understanding. This holds especially true for ruthenaelectrocatalysis, which continues to be underdeveloped. Thus, a plethora of ruthenium-catalyzed C–H activations with chemical oxidants[9] is contrasted by only a few examples of ruthenaelectrocatalysis.[10] Within our program on electrochemical C–H activation,[11] we have now developed a ruthenium-catalyzed electrochemical dehydrogenative alkyne annulation by imidazoles that assembles a variety of bridgehead *N*−fused [5,6]-bicyclic heteroarenes (Figure 1). Notably, a novel aza-ruthena(II)-bicyclo-[3.2.0]-heptadiene was identified as the key intermediate, which undergoes oxidation induced reductive elimination. This motif provides first structural proof for an unprecedented mechanistic manifold for annulations – even beyond the generally accepted metallalkenyl, metallacyclopropene, and recently proposed metallallylcarbenoid intermediates.[12] Salient features of our findings include 1) ruthenaelectro-catalytic alkenylic[8c] and aryl C–H functionalization, 2) alkyne annulations for *N*−fused [5,6]-bicyclic heteroarenes, 3) isolation and full characterization of a novel aza-ruthena(II)-bicyclo-[3.2.0]-heptadiene and 4) mechanistic insights into oxidation-induced reductive elimination[13] at ruthenium(II) by experiments and calculation.

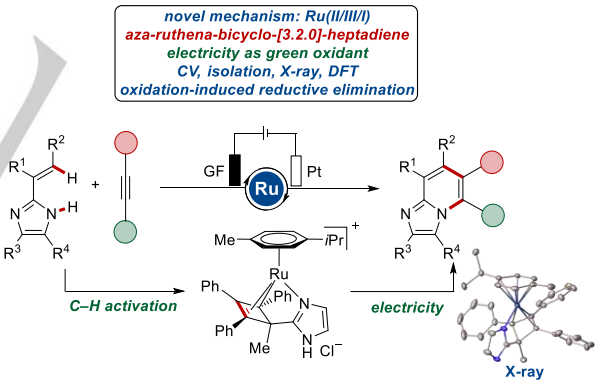

Figure 1. Novel mechanism for electrooxidative C–H activation by aza-ruthena(II)-bicyclo-[3.2.0]-heptadienes.

Results and Discussion

At the outset of our studies, we explored various reaction conditions for the envisioned ruthenium-catalyzed electro-oxidative C–H/N–H activation of alkenyl imidazole **1a** with alkyne **2a** in an operationally simple undivided cell setup equipped with a GF (graphite felt) anode and a Pt cathode (Table 1 and see Table S-1 in the Supporting Information).[14] After considerable preliminary experimentation, we observed that the desired product **3aa** was indeed obtained by catalytic amounts of $[RuCl_2(p\text{-cymene})]_2$, along with KPF_6 as the optimal catalytic additive, while among various solvents, the best results were

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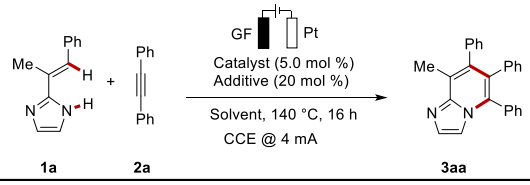
observed in DMF (entries 1–5). The yield was reduced when sodium salts were used, such as NaCl and $NaPF_6$ (entries 6–7). Gratifyingly, reducing the reaction time to 8 h led to the same yield of product **3aa** (entry 8). A reaction conducted with a Pt anode instead of GF resulted in a sharp drop in yield (entry 10). The addition of the redox mediator of BQ did not improve the performance of the ruthenium catalyst (entries 11–12). Control experiments verified the essential role of the electricity, the additive and the ruthenium catalyst (entries 13–15). A set of otherwise typical transition metal catalysts were also probed, but gave none or significantly reduced amounts of product **3aa** (entries 16–20).

Table 1. Optimization of ruthenaelectro-catalyzed annulation.[a]

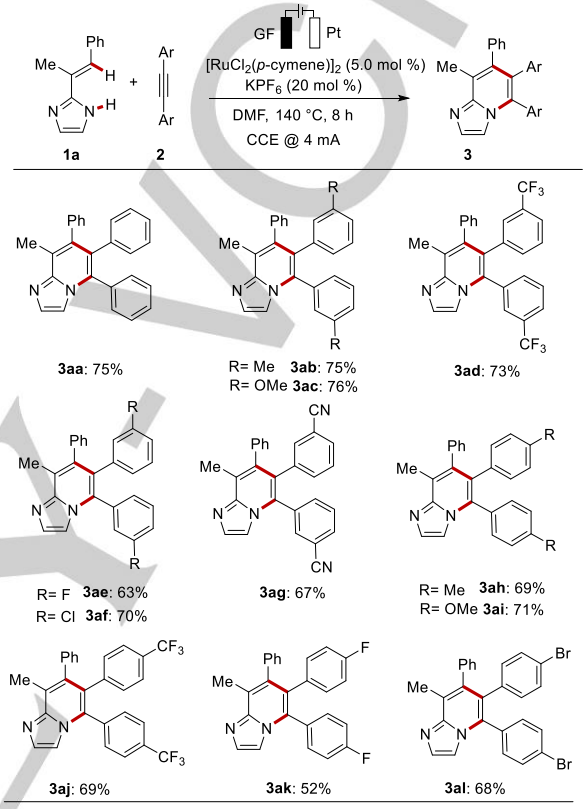


1a 2a 3aa

Entry	Catalyst	Additive	Solvent	Yield [%][b]
1	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	MeOH	10%[c]
2	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	*t*-AmOH/H_2O	12%[d]
3	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DMA	33%
4	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	NMP	10%
5	**$[RuCl_2(p\text{-cymene})]_2$**	**KPF_6**	**DMF**	**75%**
6	$[RuCl_2(p\text{-cymene})]_2$	NaCl	DMF	50%
7	$[RuCl_2(p\text{-cymene})]_2$	$NaPF_6$	DMF	66%
8	**$[RuCl_2(p\text{-cymene})]_2$**	**KPF_6**	**DMF**	**75%[e]**
9	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DMF	56%[f]
10	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DMF	46%[g]
11	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DMF	33%[h]
12	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DMF	28%[i]
13	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DMF	10%[j]
14	$[RuCl_2(p\text{-cymene})]_2$	---	DMF	50%
15	---	KPF_6	DMF	---
16	Ru(*p*-cymene)$(OAc)_2$	KPF_6	DMF	53%
17	$Co(OAc)_2{\cdot}4H_2O$	KPF_6	DMF	---
18	$[Cp^*RhCl_2]_2$	KPF_6	DMF	36%
19	$[Cp^*IrCl_2]_2$	KPF_6	DMF	10%
20	$Pd(OAc)_2$	KPF_6	DMF	---

[a] Reaction conditions: Undivided cell, **1a** (0.40 mmol), **2a** (0.80 mmol), catalyst (5.0 mol %), additive (20 mol %), solvent (4.0 mL), 140 °C, 16 h,constant current at 4.0 mA, GF anode, Pt-plate cathode. [b] Yields of isolated product. [c] 60 °C. [d] *t*-AmOH/H_2O = 1/1, 100 °C. [e] 8 h. [f] 5 h. [g] Pt-plate as anode. [h] BQ (10 mol %). [i] BQ (10 mol %), 100 °C. [j] no electricity. DMF = *N,N*-Dimethylformamide, BQ = 1,4-Benzoquinone.

Having identified the optimal reaction conditions, we explored the versatility of our electrochemical annulation with diversely decorated alkynes **2** (Scheme 1). Electron-rich as well as electron-deficient aromatic moieties at the alkynes **2** were amenable to the ruthenaelectro-catalyzed C–H functionalizations. Thereby, a variety of synthetically useful electrophilic functional groups, such as chloro (**3af**), cyano (**3ag**) and bromo (**3al**) substituents, were fully tolerated, which should prove invaluable for late-stage manipulation.



Scheme 1. Electrochemical C–H/N–H activation with alkynes **2**.

We next turned our attention to diversified alkenyl imidazoles **1** (Scheme 2). Imidazoles **1b–f** bearing a range of substituents at different sites on the alkene or the imidazole were effectively transferable to deliver products **3ba–3fa**. In addition, benzimidazole substrates with a β-methyl group (**1g**) and without a β-substituent on the alkene (**1h**) were effective for C–H/N–H activation. Notably, thiophenyl substituted benzimidazole **1i** also was a competent substrate, giving the corresponding annulation product **3ia** with high efficacy.

The ruthenaelectro-catalyzed dehydrogenative alkyne annulation regime was not restricted to alkenyl imidazoles **1**. Indeed, we next investigated the generality of the metallaelectrocataylsis by the assembly of the benzimidazoisoquinoline skeleton **5** (see Table S2 for optimization) through annulation of alkynes **2** by 2-arylimidazoles **4** (Scheme 3). Substitution at the 2-aryl group (**4b–4i**) and the benzimidazole (**4l–4m**) gave the desired benzimidazo-isoquinolines. Likewise, 2-naphthylbenzimidazole (**4j**) and 2-phenylnaphthoimidazole (**4k**) also afforded the corresponding products. The unsymmetrical 1-phenyl-1-propyne **2m** gave the product **5am** with high levels of regioselectivity. Importantly,

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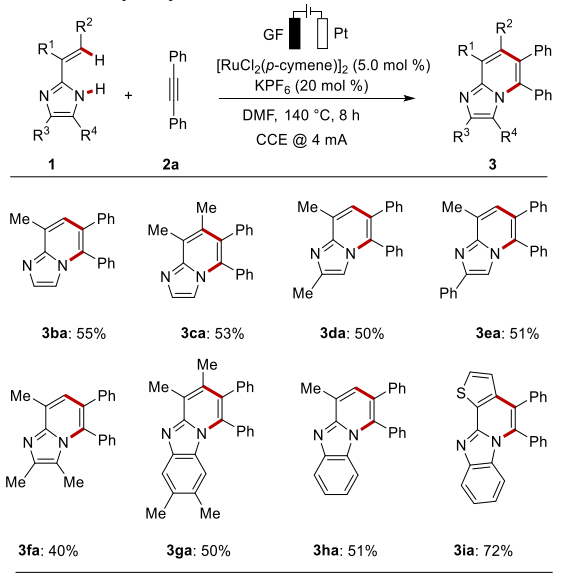
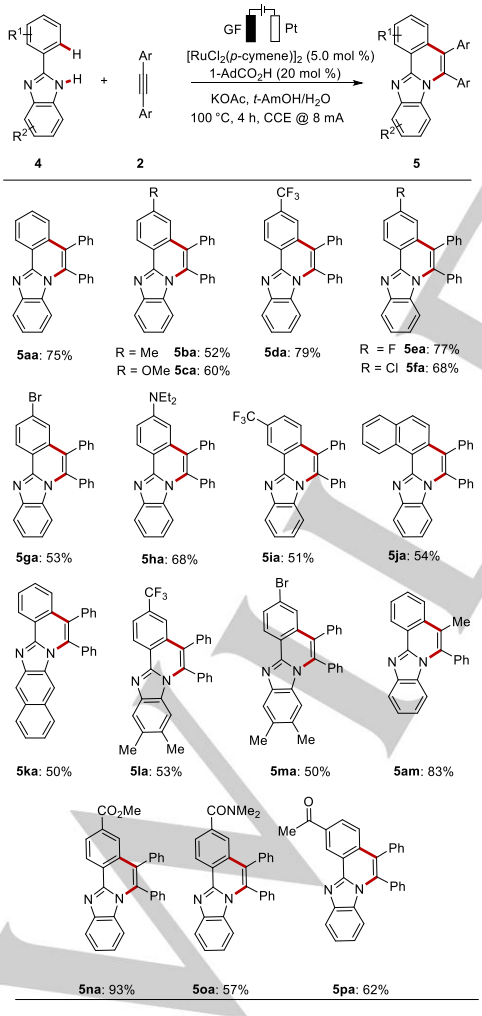
chloro, bromo, ester, amide and enolizable ketone substituents were thereby fully tolerated.

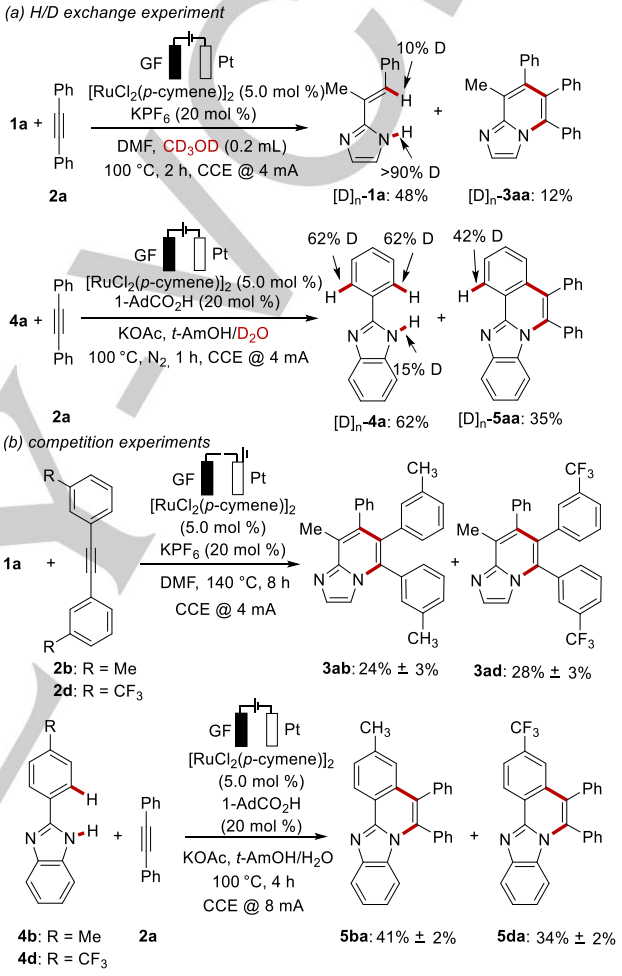


Scheme 2. Electrochemical alkyne annulation by alkenyl imidazoles **1**.



Scheme 3. Electrooxidative C–H activation of benzimidazoles **4**.

Intrigued by the ruthenaelectro-catalyzed C–H/N–H functionalization, we became attracted to delineating the catalyst's mode of action. To this end, reactions with isotopically labeled solvent were suggestive of a fast C–H cleavage, occurring by an organometallic C–Ru bond formation (Scheme 4a). Intermolecular competition experiments revealed a slight preference for electron-poor alkynes **2** and electron-rich arenes **4** (Scheme 4b). Molecular H_2 is generated as the by-product through cathodic proton reduction, which was confirmed by head-space GC analysis.[14]



Scheme 4. Summary of key mechanistic experiments.

Next, we probed the isolation of intermediates by stoichiometric experimentation. Thus, we first selectively prepared the ruthenacycle **Ru-II** (Scheme 5a). Second, the ruthenacycle **Ru-II** delivered upon stoichiometric reaction with alkynes **2** the unprecedented aza-ruthena(II)-bicyclo-[3.2.0]-heptadienes **Ru-IVa** and **Ru-IVb**, which were unambiguously characterized by X-ray diffraction analysis. Notably, the metallacyles **Ru-II** and **Ru-IV** proved to be competent under catalytic reaction conditions also (Scheme 5b). It is noteworthy that the aza-ruthena(II)-bicyclo-[3.2.0]-heptadiene **Ru-IVa** was stable, but gave the product **3aa** upon electrolysis, being suggestive of an oxidation-induced reductive elimination within a ruthenium(II/III) manifold.

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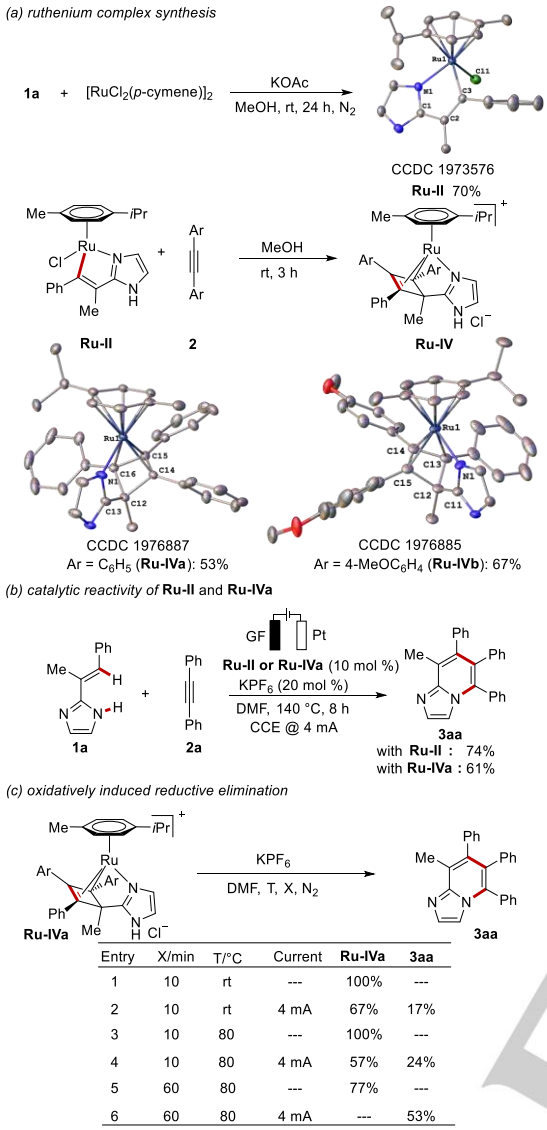

Entry	X/min	T/°C	Current	Ru-IVa	3aa
1	10	rt	---	100%	---
2	10	rt	4 mA	67%	17%
3	10	80	---	100%	---
4	10	80	4 mA	57%	24%
5	60	80	---	77%	---
6	60	80	4 mA	---	53%

Scheme 5. X-ray crystal structure analysis and applications. Selected bond lengths [Å]: **Ru-II:** Ru1-N1: 2.086(3), Ru1-C3: 2.083(3), N1-C1: 1.340(4), C1-C2: 1.446(4), C2-C3: 1.356(4); **Ru-IVa**: Ru1-N1: 2.101(2), Ru1-C14: 2.172(3), Ru1-C15: 2.171(3), Ru1-C16: 2.222(3), N1-C13: 1.326(4), C12-C13: 1.481(4), C12-C14: 1.577(4), C12-C16: 1.564(4), C14-C15: 1.442(4), C15-C16: 1.449(4); **Ru-IVb**: Ru1-N1: 2.094(3), Ru1-C13: 2.220(3), Ru1-C14: 2.185(3), Ru1-C15: 2.174(3), N1-C11: 1.333(4), C11-C12: 1.477(4), C12-C13: 1.557(4), C12-C15: 1.587(4), C13-C14: 1.446(5), C14-C15: 1.449(5).

Furthermore, we probed the electrochemical C–H activation by means of cyclovoltammetric analysis of the well-defined ruthenacycles (Figure 2). Thus, we observed at ambient temperature an irreversible oxidation of the ruthenium(II) complex **Ru-II** at E_p = 0.60 V *vs.* SCE. The aza-ruthena(II)-bicyclo-[3.2.0]-heptadiene **Ru-IVa** featured a considerably higher oxidation wave at E_p = 1.20 V *vs.* SCE, both of which could be rationalized by an oxidation-induced reductive elimination within a ruthenium(II/III) regime.

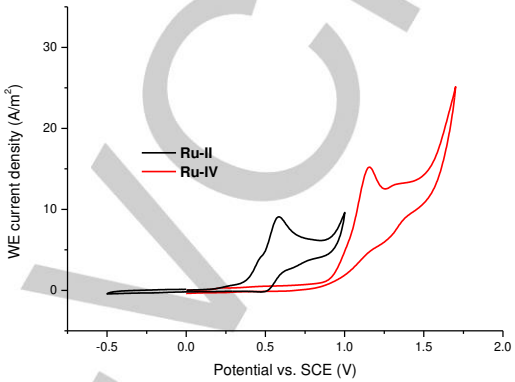

Figure 2. Cyclic voltammetry in DMF with 100 mM KPF_6 under N_2 at RT with 100 mV/s of **Ru-II** (5 mM) and **Ru-V** (5 mM).

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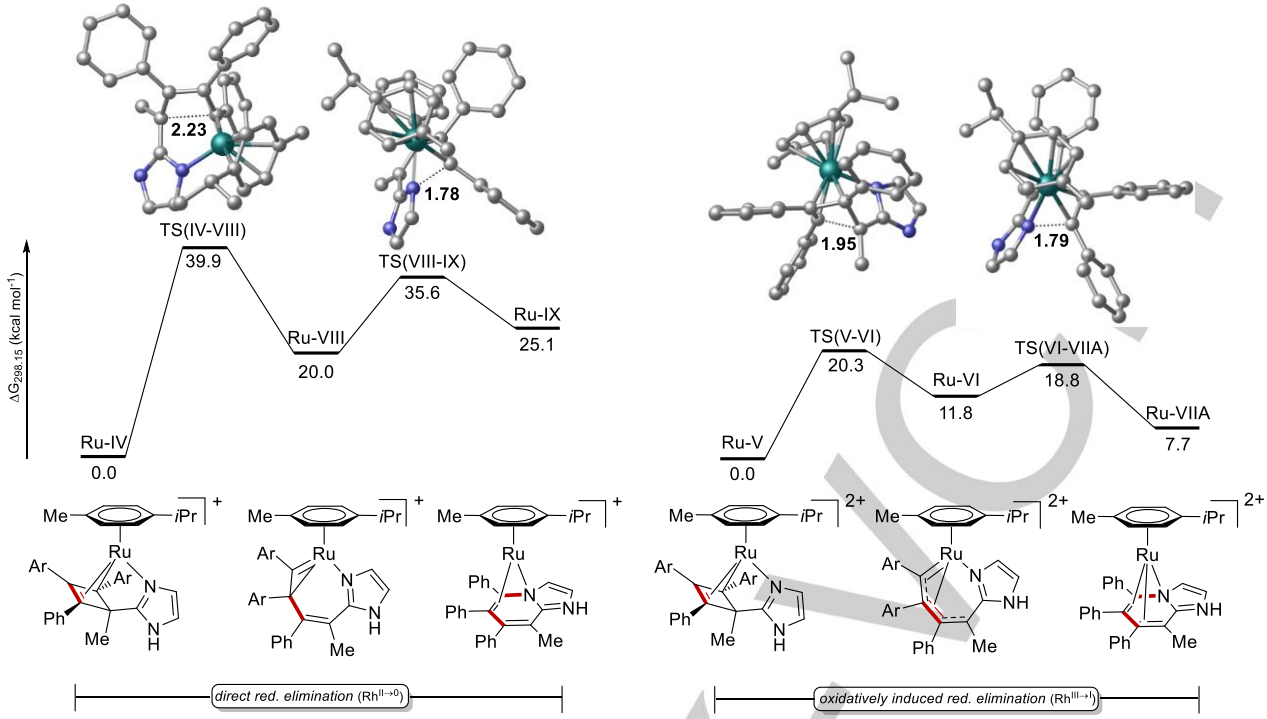
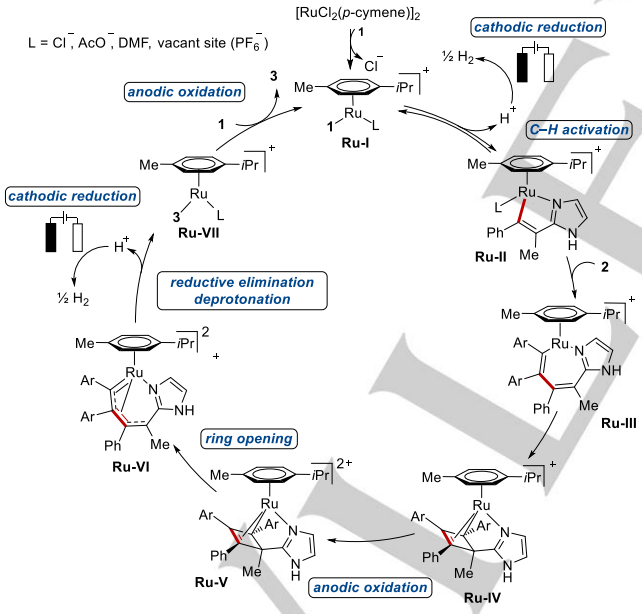


Figure 3. Relative Gibbs free energy profile in kcal·mol^{-1} comparing the direct reductive elimination and oxidatively induced reductive elimination pathways at the PBE0-D3(BJ)/6-311++G(d,p),def2-TZVP(Ru),SDD(Ru)+SMD(DMF)//TPSS-D3(BJ)/6-31G(d),def2-SVP(Ru),SDD(Ru) level of theory. Non-participating hydrogen atoms were omitted for clarity. The bond distances in the transition states are given in angstrom.



Scheme 6. Proposed catalytic cycle.

Further, we have compared the direct reductive elimination at the aza-ruthena(II)-bicyclo-[3.2.0]-heptadiene with the oxidatively-induced reductive elimination at ruthenium(III) **Ru-IV** and **Ru-V** at the PBE0-D3(BJ)/6-311++G(d,p),def2-TZVP(Ru), SDD(Ru)+SMD(DMF)//TPSS-D3(BJ)/6-31G(d),def2-SVP(Ru), SDD(Ru) level of theory (Figure 3). Thus, our computational findings confirmed the preferential reductive elimination at ruthenium(III), being indicative of a ruthenium(II/III/I) manifold.

Based on our mechanistic studies, we propose a plausible catalytic cycle to commence by a fast organometallic C–H activation (Scheme 6). Thereby, ruthena(II)cycle **Ru-II** is generated.[15] Thereafter, alkyne coordination and migratory insertion furnish the aza-ruthena-bicyclo-[3.2.0]-heptadiene **Ru-IV**, which undergoes anodic oxidation to deliver the ruthenium(III) complex **Ru-V**. Subsequent pericyclic ring opening yields ruthenium(III) complex **Ru-VI.** Oxidation-induced reductive elimination forms ruthenium(I) complex **Ru-VII**, which is anodically reoxidized.

Conclusion

In conclusion, we have reported on the electrocatalytic organometallic C–H/N–H functionalization of imidazoles. Novel aza-ruthena-bicyclo-[3.2.0]-heptadienes were identified as the key intermediate, setting the stage for alkyne annulations from synthetically meaningful alkenyl and aryl imidazoles with ample scope. The C–H activation employed electricity as the only oxidant and generated molecular hydrogen as the sole byproduct. Mechanistic studies by experiment and DFT provided strong support for an oxidation-induced reductive elimination of aza-ruthena-bicyclo-[3.2.0]-heptadienes by environmentally-benign electricity. These findings should prove instrumental for the mechanistic understanding and catalyst design of ruthenium(II)-catalyzed oxidative C–H activations.

Acknowledgements

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

Keywords: ruthenium • C–H activation • dehydrogenation • electrochemistry • *N*–heterocycles

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10.1002/anie.202000762

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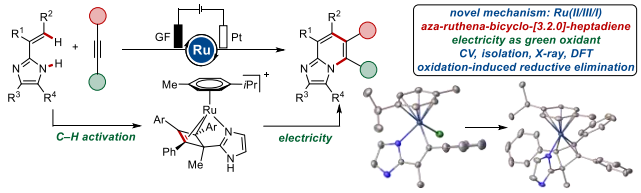

New mechanism: Aza-ruthena-bicyclo-[3,2,0]-heptadienes as key intermediates for ruthena(II/III)electro-catalyzed C–H activation.

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