Azaruthen(a)II)-bicyclo[3.2.0]heptadiene: Key Intermediate for Ruthenaelectro(II/III/I)-catalyzed Alkyne Annulations

Long Yang, Ralf Steinbock, Alexej Scheremetjew, Rositha Kuniyil, Lars H. Finger, Antonis M. Messinis, and Lutz Ackermann*

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 azaruthena(II)-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 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 have emerged as useful tools 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] are 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 mechanism for electrooxidative C–H activation by azaruthen(a)II)-bicyclo[3.2.0]heptadienes. CV = cyclic voltammetry, DFT = density functional theory, GF = graphite felt.

Figure 1. Novel mechanism for electrooxidative C–H activation by azaruthen(a)II)-bicyclo[3.2.0]heptadienes. CV = cyclic voltammetry, DFT = density functional theory, GF = graphite felt.

Results and Discussion

At the outset of our studies, we explored various reaction conditions for the envisioned ruthenium-catalyzed electrooxidative C–H/N–H activation of alkynyl 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). \[\text{DMF 46}\]
\[\text{KPF}\]
\[\text{NaPF}\]
\[\text{MeOH 10}\]
\[\text{DMF 10}\]
\[\text{KPF}\]
\[\text{entries 16–20}\]. \[\text{DMF 33}\]
\[\text{DMF 75}\]
\[\text{DMF 66}\]
\[\text{KPF}\]
\[\text{Electrochemical alkyne annulation by alkenyl imidazoles}\]
\[\text{3a a}\]
\[\text{Optimization of ruthenaelectrocatalyzed annulation.}\]
as the optimal catalytic additive, while among various \[\text{Electrochemical C}_{KPF}\]
\[\text{KPF}\]
\[\text{3a a}\]
\[\text{0.40 mmol}\], \[\text{DMF 10}\]
\[\text{KPF}\]
\[\text{DMF –}\]
\[\text{KPF}\]
\[\text{T}\]
\[\text{KPF}\]
\[\text{2}\]
\[\text{DMF 56}\]
\[\text{KPF\textsuperscript{2}}\]
\[\text{DMF 28}\]
\[\text{KPF}\]
\[\text{KPF}\]
\[\text{59}\]
\[\text{DMA 33}\]
\[\text{KPF}\]
\[\text{t}\]
\[\text{KPF}\]
\[\text{2020}\]
\[\text{The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim}\]
\[\text{www.angewandte.org}\]
\[\text{Table 1: Optimization of ruthenaelectrocatalyzed annulation.}\]
\begin{table}[h]
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Catalyst & Additive & Solvent & Yield [%]\tabularnewline
\hline
1 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{MeOH} & 10\textsuperscript{[f]}\tabularnewline
2 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{i-AmOH/H\textsubscript{2}O} & 12\textsuperscript{[h]}\tabularnewline
3 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{DMA} & 33\tabularnewline
4 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{NMP} & 10\tabularnewline
5 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{DMF} & 75\tabularnewline
6 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{NaCl} & \text{DMF} & 50\tabularnewline
7 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{NaPF\textsubscript{6}} & \text{DMF} & 66\tabularnewline
8 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{DMF} & 75\textsuperscript{[i]}\tabularnewline
9 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{DMF} & 56\textsuperscript{[j]}\tabularnewline
10 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{DMF} & 46\textsuperscript{[k]}\tabularnewline
11 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{DMF} & 33\textsuperscript{[l]}\tabularnewline
12 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{DMF} & 28\textsuperscript{[m]}\tabularnewline
13 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & \text{KPF\textsubscript{5}} & \text{DMF} & 10\textsuperscript{[n]}\tabularnewline
14 & \text{[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}} & – & \text{DMF} & 50\tabularnewline
15 & – & \text{KPF\textsubscript{5}} & \text{DMF} & –\tabularnewline
16 & \text{Ru(p-cymene)(OAc)} & \text{KPF\textsubscript{5}} & \text{DMF} & 53\tabularnewline
17 & \text{Co(OAc)}\textsubscript{2}·4\textsubscript{H\textsubscript{2}O} & \text{KPF\textsubscript{5}} & \text{DMF} & –\tabularnewline
18 & \text{[Cp*RhCl\textsubscript{2}]} & \text{KPF\textsubscript{5}} & \text{DMF} & 36\tabularnewline
19 & \text{[Cp*RhCl\textsubscript{2}]} & \text{KPF\textsubscript{5}} & \text{DMF} & 10\tabularnewline
20 & \text{Pd(OAc)} & \text{KPF\textsubscript{5}} & \text{DMF} & –\tabularnewline
\hline
\end{tabular}
\end{table}
\[\text{Scheme 1. Electrochemical C–H/N–H activation with alkynes 2.}\]
\[\text{Scheme 2. Electrochemical alkyne annulation by alkenyl imidazoles 1.}\]

Having identified the optimal reaction conditions, we explored the versatility of our electrochemical annulation with diversely decorated alkynes 2 (Scheme 1). Alkynes 2 with electron-rich as well as electron-deficient aromatic moieties were amenable to the ruthenaelectrocatalyzed 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.

We next turned our attention to diversified alkenyl imidazoles 1 (Scheme 2). Imidazoles 1b-f bearing a range of electrophilic functional groups, such as chloro (3af), cyano (3ag) and bromo (3al) substituents, were fully tolerated, which should prove invaluable for late-stage manipulation.
of substituents at different sites on the alkene or the imidazole were effectively transferable to deliver products \(3b_a-3f_a\). In addition, benzimidazole substrates with a \(\beta\)-methyl group (1g) and without a \(\beta\)-substituent on the alkene (1h) were effective for C-H/N-H activation. Notably, thienophenyl-substituted benzimidazole 1i was also a competent substrate, giving the corresponding annulation product \(3i_a\) with high efficacy.

The ruthenaelectrocatalyzed dehydrogenative alkyne annulation regime was not restricted to alkenyl imidazoles 1. Indeed, we next investigated the generality of the metal-laelectrocatalysis by the assembly of the benzimidazoisoquinoline skeleton 5 (see Table S2 for optimization) through annulation of alkynes 2 by 2-arylimidazoles 4 (Scheme 3). Substrates with substitution at the 2-aryl group (4b–4i) and the benzimidazole (4l–4m) gave the desired benzimidazoisoquinolines. 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, chloro, bromo, ester, amide, and enolizable ketone substituents were thereby fully tolerated.

Intrigued by the ruthenaelectrocatalyzed C-H/N-H functionalization, we decided to delineate the catalyst’s mode of action. To this end, reactions with isotopically labeled solvent were suggestive of a fast C-H cleavage, occurring by the formation of an organometallic C-Ru bond (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 byproduct through cathodic proton reduction, which was confirmed by head-space GC analysis.\(^{[14]}\)

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 azaruthena(II)-bicyclo[3.2.0]heptadienes Ru-IVA and Ru-IVb, which were unambiguously characterized by X-ray diffraction analysis. Notably, the metallacycles Ru-II and Ru-IV proved to be competent under catalytic reaction conditions also (Scheme 5b). It is noteworthy that the azaruthena(II)-bicyclo-

---

Scheme 3. Electrooxidative C-H activation of benzimidazoles 4.

Scheme 4. Summary of key mechanistic experiments.
heptadiene Ru-IVa was stable, but gave the product 3aa upon electrolysis, which is suggestive of an oxidation-induced reductive elimination within a ruthenium(II/III) manifold (Scheme 5c).

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 azaruthena(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.

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

Based on our mechanistic studies, we propose the catalytic cycle to commence by a fast organometallic C–H activation (Scheme 6). Thereby, ruthenia(II)cycle Ru-II is generated.\[15\]

![Scheme 5. X-ray crystal structure analysis (thermal ellipsoids at 50% probability) and applications.](image)

**Scheme 5.** X-ray crystal structure analysis (thermal ellipsoids at 50% probability) and applications.\[16\] Selected bond lengths [Å]: Ru-II: Ru1-N1 2.086(3), Ru1-C1 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-C1 1.326(4), C1-C2 1.481(4), C2-C3 1.577(4), C2-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-C13 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).

[3.2.0]heptadiene Ru-IVa was stable, but gave the product 3aa upon electrolysis, which is suggestive of an oxidation-induced reductive elimination within a ruthenium(II/III) manifold (Scheme 5c).

![Scheme 6. Proposed catalytic cycle.](image)

**Scheme 6.** Proposed catalytic cycle.
Thereafter, alkyne coordination and migratory insertion furnish the azaruthenabicyclo[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-VL. 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 azaruthenabicyclo[3.2.0]heptadienes were identified as the key intermediate, setting the stage for alkyne annihilations 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 azaruthenabicyclo[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

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

Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H activation · dehydrogenation · electrochemistry · nitrogen heterocycles · ruthenium

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 are omitted for clarity. The bond lengths in the transition states are given in Ångström.

Reference:

[1] a) S. Rej, Y. Ano, N. Chatani, Chem. Rev. 2020, 120, 1788–1887; b) A. Dey, S. K. Sinha, T. K. Achar, D. Maity, Angew. Chem. Int. Ed. 2019, 58, 10820–10843; Angew. Chem. 2019, 131, 10934–10958; c) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, Chem. Rev. 2019, 119, 2192–2452; d) Y. Park, Y. Kim, S. Chang, Chem. Rev. 2017, 117, 9247–9301; e) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, Chem. Rev. 2017, 117, 8754–8786; f) B. Ye, N. Cramer, Acc. Chem. Res. 2015, 48, 1308–1318; g) O. Daugulis, J. Roane, L. D. Tran, Acc. Chem. Res. 2015, 48, 1053–1064; h) B. Li, P. H. Dixneuf, Chem. Soc. Rev. 2013, 42, 5744–5767; i) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Eillman, Acc. Chem. Res. 2012, 45, 814–825, and references therein.
