Rhoda-Electrocatalyzed Bimetallic C–H Oxygenation by Weak O-Coordination

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In memory of Professor Jean-Michel Savéant

Abstract: Rhodium-electrocatalyzed arene C–H oxygenation by weak O-coordinating amides and ketones have been established by bimetallic electrocatalysis. Likewise, diverse dihydrooxazinones were selectively accessed by the judicious choice of current, enabling twofold C–H functionalization. Detailed mechanistic studies by experiment, mass spectroscopy and cyclovoltammetric analysis provided support for an unprecedented electrooxidation-induced C–H activation by a bimetallic rhodium catalysis manifold.

Introduction

During the past decade, transition metal-catalyzed C–H activation has been recognized as a transformative tool in molecular syntheses.[1] Phenols featuring an ortho-substituted carbonyl group constitute important structural motifs of a diversity of bioactive molecules, ranging from natural products to drugs molecules.[2] Transition metal-catalyzed C–H activation by weak chelation assistance provides a straightforward access to the assembly of phenols.[3] Pioneering studies with palladium catalysis were accomplished by Dong[4] and Rao.[5] In the same year, our group reported sustainable ruthenium-catalyzed C–H oxygenations with a diverse range of weakly coordinating groups.[6] In addition, considerable efforts have been devoted to the development of different metal catalysts, along with various oxidants.[7] Despite indisputable advances, stoichiometric amounts of strong chemical oxidants, such as (diacetoxyiodo)benzene and K₂S₂O₈, are required, which leads to undesired byproducts.

Electrochemical synthesis has undergone a renaissance in recent years towards environmentally-benign organic synthesis.[8] 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.[9] Although transition metal-catalyzed electrochemically C–H oxygenation have been recently realized,[10] this mostly required strong N-coordination, such as bidentate quinolinyl amides or pyridines, while the very recently devised ruthenium catalysis needed rather costly aryl iodides as additional redox mediators, jeopardizing the inherent atom-economy.[10a] In contrast, the redox direct—mediator-free—oxidation of homogeneous metal oxygenation catalysts at the anode surface typically called for a divided cell setup.[10b–e] Within our program on electrochemical C–H activation,[11] we have now devised mechanistically-distinct rhoda-electrocatalyzed C–H oxygenations of weakly-O-coordinating amides and ketones (Figure 1). Salient features of our findings include 1) undivided cell without redox mediator, 2) room temperature oxygenations, 3) electricity in lieu of strong oxidants, 4) high Faraday efficiency, 5) twofold electrochemical C–H functionalization towards dihydrooxazinones[12] and 6) detailed mechanistic support for a bimetallic electrocatalysis manifold.

Results and Discussion

At the outset of our studies, various reaction conditions were explored for the envisioned redox-mediator-free, rhoda-electrocatalyzed C–H oxygenation of 1a in an operationally

Figure 1. Rhoda-electrocatalyzed C–H oxygenation.
simple undivided cell equipped with a graphite felt (GF) anode and a platinum cathode (Table 1 and Table S1 in the Supporting Information).[13] Preliminary experimentation indicated that nBuNPF₆ was the optimal additive (Table 1, Entries 1–4). Further studies revealed that the reaction was viable at ambient temperature (Entries 5–6) in a solvent mixture of trifluorouracil acid (TFA) and trifluoroacetic anhydride (TFAA) (1:1) (Entries 6–8). Control experiments showed that both the rhodium catalyst and electricity were essential (Entries 9–11). During the optimization, we found that NEt₃ could significantly improve the conductivity (Table S1). Thus we employed easily available TFA·NEt₃ salt (Entry 12).[14] enabling the use of a solvent mixture TFA/ TFAA (1:20) without solubility or conductivity problems (Entries 12–13 vs. Entry 8). Here, the highest yield of 82% was obtained with 2 mA (Entry 13). Interestingly, while [Rh(OAc)₃] showed high catalytic efficacy, the commonly used [RhCpCl₂] or RhCl₃·3H₂O provided unsatisfactory results (Entry 14).

With the optimized reaction conditions in hand, we next examined the viable substrate scope of the rhodium-catalyzed electrochemical C–H oxygenation with various weakly coordinating Weinreb amides 1 (Scheme 1a). Electro-rich as well as electron-deficient Weinreb amides 1a–1p were amenable to the rhodium-catalyzed electrochemical catalysis. Notably, a diverse array of valuable functional groups, including ester (2f), halogen (2g–2j) and ketone (2k) groups, were tolerated by the electrocatalysis, highlighting a notable potential for further late-stage diversification. It is noteworthy that the rhoda-electrocatalysis was not limited to Weinreb amides 1. Indeed, differently substituted amides 3a–m were also efficiently converted into the corresponding oxygenated amides 4a–m with remarkable catalytic efficiency (Scheme 1b).

The outstanding robustness of the rhoda-electrocatalyzed C–H oxygenation was further highlighted by its ability to transform more challenging ketones 5 (Scheme 2). During our optimization studies, small amounts of N-demethylation product 7a could often be isolated (Scheme 3a). Hence, we rationalized that it was formed through a cascade C–H oxygenation, along with Shono-type oxidation to generate 9. Further experimentation at O ≥ 4 F mol⁻¹ revealed small amounts of an interesting dihydrooxazinone.

**Table 1**: Optimization of the rhoda-electrocatalyzed C–H oxygenation.[a]

| Entry | Electrolyte | TFA/TFAA | I [mA] | t [h] | T [°C] | Yield [%] |
|-------|-------------|-----------|--------|------|--------|-----------|
| 1     | CF₃COONa    | 3:1       | 4       | 16   | 50     | trace     |
| 2     | LiClO₄      | 3:1       | 4       | 16   | 50     | 24        |
| 3     | nBuNBF₄     | 3:1       | 4       | 16   | 50     | 22        |
| 4     | nBuNPF₆     | 3:1       | 4       | 16   | 50     | 28        |
| 5     | nBuNPF₆     | 1:1       | 4       | 16   | 50     | 42        |
| 6     | nBuNPF₆     | 1:1       | 4       | 16   | RT     | 54        |
| 7     | nBuNPF₆     | 1:2       | 4       | 16   | RT     | 52        |
| 8     | nBuNPF₆     | 1:3[^h]   | 4       | 16   | RT     | trace[^i] |
| 9     | nBuNPF₆     | 1:1       | 1       | 16   | RT     | ND        |
| 10    | nBuNPF₆     | 1:1       | 4       | 16   | RT     | trace[^i] |
| 11    | TFA·NEt₃[^i]| 1:20      | 4       | 8    | RT     | 57[^ii]  |
| 12    | TFA·NEt₃[^i]| 1:20      | 4       | 15   | RT     | 82[^ii]  |
| 13    | TFA·NEt₃[^i]| 1:20      | 2       | 15   | RT     | 52[^ii]  |
| 14    | TFA·NEt₃[^i]| 1:20      | 2       | 15   | RT     | ND[^ii]  |
| 15    | nBuNPF₆     | 3:1       | 4       | 16   | 50     | 28[^ii]  |
| 16    | TFA·NEt₃[^i]| 1:20      | 2       | 15   | RT     | 52[^ii]  |

[a] 1 (0.5 mmol), [Rh(OAc)₃] (2.5 mol%), electrolyte (0.1 M), TFA/ TFAA, GF anode (10 mm × 10 mm × 6 mm), Pt cathode (10 mm × 15 mm × 0.125 mm). [b] Poor conductivity due to poor solubility of electrolyte. [c] Without [Rh(OAc)₃]. [d] Under N₂. [e] TFA·NEt₃ (0.33 M). [f] [RhCpCl₂] or RhCl₃·3H₂O instead of [Rh(OAc)₃] as the catalyst. [g] Ru(OAc)₃( ) as the catalyst. [h] [Rh(OPiv)₂] as the catalyst. [i] Piv = pivalate.

**Scheme 1.** Rhoda-electrocatalyzed C–H oxygenation of amides 1 and 3.

**Table S1**

| Electrolyte | TFA/TFAA | I [mA] | t [h] | Yield [%] |
|-------------|-----------|--------|------|-----------|
| TFA·NEt₃   | 1:20      | 4      | 15   | 82        |
| TFA·NEt₃   | 1:20      | 2      | 15   | 52        |
| TFA·NEt₃   | 1:20      | 2      | 15   | ND        |
| TFA·NEt₃   | 1:20      | 2      | 15   | 52[^ii]  |

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Through rational design of the work up process with NEt$_3$ as non-nucleophilic base, Int2 could be exclusively converted to the valuable dihydrooxazinone 8a (Scheme 3a, blue path). With the optimized reaction conditions, we explored the substrate scope of the rhoda-electrocatalyzed cascade reaction with diverse amides 1 and 3 to assemble various dihydrooxazinones 8 and 9 (Scheme 3b). The tolerance of ester (8f) and halogen (8g, 8i, 8p, 9d–e, 9h) substituents provides an invaluable asset in terms of late-stage modifications.

Promysalin is a Pseudomonad secondary metabolite that exhibits narrow-spectrum antibacterial activity, originally isolated from the rhizosphere (Scheme 4a).[15] In 2016, Wuest reported the total synthesis of Promysalin analogues.[15b] The key proline-salicylate fragment in Promysalin inspired us to apply our rhoda-electrocatalyzed C–H oxygenation to the synthesis of various substituted proline-salicylates (4n–p) without any protection and deprotection of the phenol motif (Scheme 4b). Next, we studied the efficiency of the catalysis with bromo analog 3p through the gram-scale synthesis with only 0.5 mol% of [Rh(OAc)$_2$]$_2$ with a turnover number of 166 based on the rhodium-dimer, along with the solvent TFAA being recovered by simple distillation, highlighting the practical potential of this catalysis (Scheme 4c).

Given the versatility of the redox mediator-free electrochemical C–H oxygenation, we became attracted to probing its mode of action. Reactions conducted with isotopically labeled [D]$_1$-TFA did not lead to any H/D scrambling.[13] Kinetic studies provided strong support for a fast C–H metalation with a minor kinetic isotope effect (KIE) of $k_H/k_D \approx 1.1$ (Scheme 5a). Then, we explored the current dependence of the performance within a range from 2.0 to 5.0 mA,

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**Scheme 2.** Rhoda-electrocatalyzed C–H oxygenation of ketones 5.

**Scheme 3.** Rhoda-electrocatalyzed cascade reaction for the synthesis of dihydrooxazinones.

**Scheme 4.** Application to the synthesis of the analogous fragments of Promysalin.
being indicative of a turnover-limiting electron transfer step in the current region of 2.0–4.0 mA (Scheme 5b). Beyond 4.0 mA the reaction rate did not increase significantly, being suggestive of a switch in the turnover-limiting step.

Next, we turned our attention to investigate the ligand exchange effect at rhodium. Somewhat surprisingly, [Rh(OTFA)$_2$]$_2$ did not show any catalytic reactivity for this electrochemical catalysis (Scheme 6a). Mass spectroscopy studies revealed a rapid OAc-/OTFA exchange in the solvent mixture TFA/TFAA (1:1), while in TFA/TFAA (1:20) this exchange was slow[13] which may be caused by the low concentration of available TFA. These observations are matched with the low catalytic activity in TFA/TFAA (1:1) (Table 1), suggesting the ligand exchange to be harmful to the catalyst activity. While stepwise electrochemical oxygenation delineated an oxidation-induced C–H activation and oxygenation, mass spectroscopic analysis of the electrolyzed mixture showed a plausible active intermediate [Rh(OAc)$_2$(OTFA)$_2$], highlighting the dimeric form of the catalyst (Scheme 6b). This was further experimentally supported by the inactivity of the monomeric Rh(OAc)$_3$ (Scheme 6c).

Furthermore, we probed an electrochemical oxidation-induced C–H activation by means of cyclovoltammetric analysis (Figure 2). First, the oxidation potential of amide being indicative of a turnover-limiting electron transfer step in the current region of 2.0–4.0 mA (Scheme 5b). Beyond 4.0 mA the reaction rate did not increase significantly, being suggestive of a switch in the turnover-limiting step.

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![Diagram](image.png)

**Scheme 5.** Key mechanistic experiments.

![Diagram](image.png)

**Scheme 6.** Mechanistic studies on rhoda-electrocatalyzed oxygenation.
1a was higher than [Rh(OAc)₂] in TFA/TFAA (1:1), suggesting an oxidation-induced C–H activation regime (Figure 2a). In TFA/TFAA (1:20), [Rh(OAc)₂] featured an onset potential of $E_{\text{onset}} = 0.8$ V vs. Ag/AgCl with low current, due to the poor solubility of [Rh(OAc)₂] (Figure 2b, dark). In TFA/TFAA (1:1), the oxidation peak shifts to higher oxidation potentials, this shift is likely caused by gradually -OAc/-OTFA ligand exchange, implying the more -OTFA substituents on rhodium, the higher oxidation potential exhibited (Figure 2b, blue). In line with this observation, [Rh(OTFA)₂] revealed a high onset potential of $E_{\text{onset}} = 1.3$ V vs. Ag/AgCl, which further rationalized as to why [Rh(OTFA)₂] was not catalytically competent (Figure 2b, red).

Likewise, the catalyst’s mode of action was investigated by means of DFT studies at the B3LYP-D4/6-311++G**,Rh/SDD + SMD(DCE)//B3LYP-D3/6-31G**,Rh/SDD level of theory. Thus, several bimetallic rhodium complexes were probed, namely monocationic (Figure S9) or dicationic (Figure 3) Rh₃⁻⁻Rh₃ as well as monocationic Rh²⁺⁻Rh³⁻⁻ (Figure S11). According to our findings, a C–H rhodation via dicaticonic Rh³⁻⁻Rh³⁻⁻ complex was identified as the most plausible pathway with an activation barrier of 25.1 kcal mol⁻¹.

On the basis of our mechanistic studies, we propose a plausible catalytic cycle to be initiated by facile electrochemical oxidation of [Rh(OAc)₂] to generate the rhodium(III)-rhodium(II) species 10 (Figure 4). A subsequent anodic oxidation generates the catalytically competent bimetallic rhodium(III) species 11. Notably, the bimetallic nature of the electrocatalysis allows for effective direct oxidations in the absence of a redox mediator. Then, isomerization and substrate coordination occur to deliver intermediate 12.

Conclusion

In conclusion, we have reported on mechanistically-distinct rhoda-electrocatalysis for C–H oxygenations of synthetically useful amides and ketones by challenging weak O-coordination. In an undivided cell, an easily accessible ionic liquid and mild reaction conditions set the stage for an operationally-friendly C–H oxygenation in the absence of redox mediators. By adjusting the current, valuable dihydrooxazines could be selectively assembled by double C–H functionalization. The application to the late-stage assembly of Promysalin analogue fragments with a low catalyst loading, as well as gram-scale bimetallic electrocatalysis accounts for the considerable practical potential. Detailed mechanistic studies revealed an oxidation-induced C–H activation by a bimetallic rhodium catalysis manifold.

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Conflict of interest
The authors declare no conflict of interest.

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[15] a) C. E. Keohane, A. D. Steele, C. Fetzer, J. Khowsathit, D. Van Tyne, L. Moyniè, M. S. Gilmore, J. Karanicolas, S. A. Sieber, W. M. Wuest, J. Am. Chem. Soc. 2018, 140, 1774–1782; b) A. D. Steele, C. E. Keohane, K. W. Knouse, S. E. Rossiter, S. J. Williams, W. M. Wuest, J. Am. Chem. Soc. 2016, 138, 5833–5836; c) A. D. Steele, K. W. Knouse, C. E. Keohane, W. M. Wuest, J. Am. Chem. Soc. 2015, 137, 7314–7317; d) W. Li, P. Estrada-de los Santos, S. Matthijs, G.-L. Xie, R. Busson, P. Cornelis, J. Rozenaki, R. De Mot, Chem. Biol. 2011, 18, 1320–1330.

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