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Electrooxidative Ruthenium-Catalyzed C–H/O–H Annulation by Weak *O*-Coordination

Youai Qiu,[a] Cong Tian,[a] Leonardo Massignan,[a] Torben Rogge,[a] and Lutz Ackermann*[a,b]

Abstract: Electrocatalysis has been identified as a powerful strategy for organometallic catalysis, but as of yet electrocatalytic C–H activation was restricted to strongly *N*-coordinating directing groups. In contrast, herein, we present the first electrocatalytic C–H activation by weak *O*-coordination. Thus, a versatile ruthenium(II) carboxylate catalyst enabled the electrooxidative C–H/O–H functionalization for alkyne annulations in the absence of metal oxidants, exploiting sustainable electricity as the sole oxidant. Mechanistic insights provided strong support for a facile organometallic C–H ruthenation and an effective electrochemical reoxidation of the key ruthenium(0) intermediate.

Electrosynthesis has emerged as an increasingly powerful tool for molecular syntheses.[1] A significant recent momentum was gained by the merger of electrocatalysis with organometallic[2] C–H activation.[3] However, despite these indisputable advances, all electrochemical C–H activations[4] are thus far limited to palladium[3] and cobalt[5] catalysts,[1b] and severely restricted by substrates bearing nitrogen-containing, strongly coordinating directing groups.[3; 5] In sharp contrast, within our program on sustainable C–H functionalization,[6] we have now developed the first electrochemical, organometallic C–H activation with synthetically-meaningful, weakly-coordinating[7] substrates, on which we report herein (Figure 1). Salient features of our findings include (i) first electrooxidative ruthenium-catalyzed[8] C–H activation, (ii) weakly coordinating benzoic acids for C–H/O–H alkyne annulations[9] with electricity as the sole oxidant, (iii) mechanistic insights on the electrochemical oxidation of the key ruthenium(0) intermediate, and (iv) C–H/N–H functionalizations by electrooxidative ruthenium catalysis.

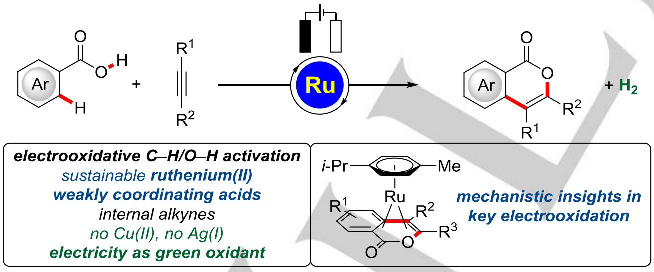
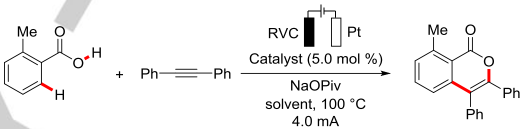


Figure 1. Electrochemical C–H activation by weak *O*-coordination.

Our studies were initiated by probing various reaction conditions for the envisioned electrooxidative C–H activation with weakly-coordinating benzoic acid **1a** (Table 1 and Table S-1 in the Supporting Information).[10] Preliminary experimentation highlighted the power of ruthenium(II) catalysis in protic polar solvents (entries 1-4). The robust ruthenium(II) carboxylate manifold was fully tolerant of air and H_2O, with optimal results being obtained in a solvent mixture of *tert*-amyl alcohol and H_2O with sodium pivalate as the additive (entries 5-10). Control experiments reflected the outstanding performance of the ruthenium(II) carboxylates[11] (entries 8-19), while typical iridium, cobalt and palladium catalyst fell short in delivering the desired product **3aa** (entries 11-15). In contrast to cobalt-catalyzed annulation process with strongly coordinating bidentate directing groups, the ruthenium catalysis enabled the conversion of internal alkynes **2**.

Table 1. Optimization of the electrochemical C–H annulation.[a]



1a **2a** **3aa**

Entry	Catalyst	Solvent	**3aa** [%][b]
1	$[RuCl_2(p\text{-cymene})]_2$	*t*AmOH	10
2	$[RuCl_2(p\text{-cymene})]_2$	H_2O	44
3	$[RuCl_2(p\text{-cymene})]_2$	TFE	35[c]
4	$[RuCl_2(p\text{-cymene})]_2$	MeOH	33[c]
5	$[RuCl_2(p\text{-cymene})]_2$	*t*AmOH/H_2O (1/1)	79
6	$[RuCl_2(p\text{-cymene})]_2$	*t*AmOH/H_2O (3/1)	25[d]
7	$[RuCl_2(p\text{-cymene})]_2$	*t*AmOH/H_2O (3/1)	27[e]
8	$[RuCl_2(p\text{-cymene})]_2$	*t*AmOH/H_2O (3/1)	85
9	$[RuCl_2(p\text{-cymene})]_2$	*t*AmOH/H_2O (7/1)	71
10	$[RuCl_2(p\text{-cymene})]_2$	*t*AmOH/H_2O (3/1)	18[f]
11	---	*t*AmOH/H_2O (3/1)	---
12	$Ru(p\text{-cymene})(OAc)_2$	*t*AmOH/H_2O (3/1)	62
13	$[Cp^*IrCl_2]_2$	*t*AmOH/H_2O (3/1)	---
14	$Cp^*Co(MeCN)_3(SbF_6)_2$	*t*AmOH/H_2O (3/1)	---
15	$Pd(OAc)_2$	*t*AmOH/H_2O (3/1)	---
16	$[Cp^*RhCl_2]_2$	*t*AmOH/H_2O (3/1)	82
17	$[RuCl_2(p\text{-cymene})]_2$	*t*AmOH/H_2O (3/1)	85[g]
18	$[RuCl_2(p\text{-cymene})]_2$	*t*AmOH/H_2O (3/1)	26[h,i]
19	$\mathbf{[RuCl_2(p\text{-cymene})]_2}$	***t*AmOH/H_2O (3/1)**	**90**[i]

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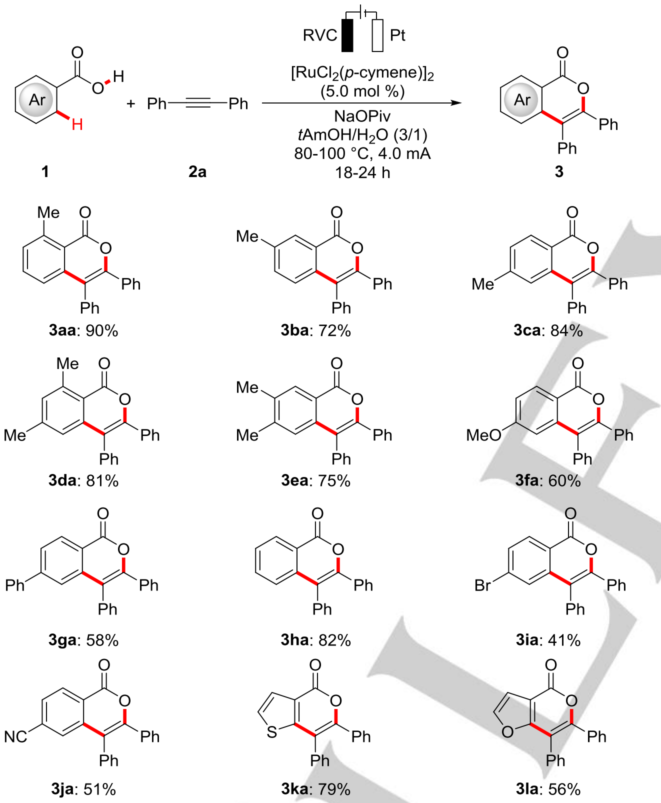
Supporting information for this article is given via a link at the end of the document.

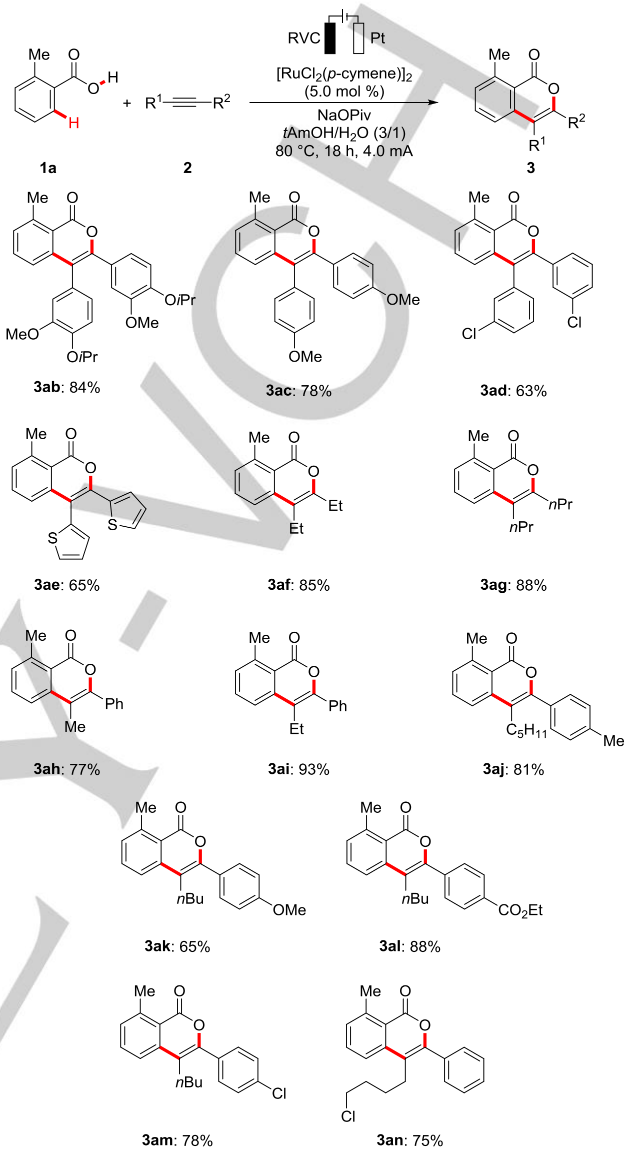
[a] Undivided cell, RVC anode, Pt cathode, constant current = 4.0 mA, **1a** (1.0 mmol), **2a** (0.5 mmol), catalyst (5.0 mol %), NaOPiv (1.0 equiv), solvent (4 mL), under air, 100 °C, 18 h. [b] Yield of isolated product. [c] 60 °C. [d] KPF_6 (1.0 equiv) as additive. [e] NaOAc (1.0 equiv) as additive. [f] No electricity. [g] Under N_2. [h] No NaOPiv. [i] 80 °C. RVC = reticulated vitreous carbon, Am = amyl.

With the optimized ruthenium(II) catalyst for the elctrooxidative C–H/O–H functionalization in hand, we tested its versatility with a set of representative benzoic acids **1** (Scheme 1). Thus, the versatile ruthenium catalysis manifold proved amenable to both electron-rich as well as electron-deficient arenes **1**. Thereby, valuable electrophilic functional groups were fully tolerated, including bromo, cyano and heterocyclic scaffolds. The site-selectivity of intramolecular competition experiments with *meta*-substituted arenes **1b** and **1e** was governed by steric interactions.



Scheme 1. Electrochemical C–H/O–H alkyne annulation by weakly coordinating acids **1**.

The broadly applicable ruthenium(II) carboxylate catalyst enabled the efficient conversion of diaryl-, diheteroaryl- and dialkyl-substituted alkynes **2** (Scheme 2). Unsymmetrical alkynes **2h**-**2n** delivered the desired products **3** with high levels of regio-control, generally placing the aromatic moiety in proximity to the oxygen heteroatom.[12] It is noteworthy that both aryl as well as reactive alkyl chlorides **2m** and **2n**, respectively, were chemo-selectively converted likewise.



Scheme 2. Electrochemical C–H/O–H annulation of alkynes **2**.

The electrochemical ruthenium-catalyzed C–H activation/alkyne annulation regime was not restricted to benzoic acids **1**. Indeed, synthetically meaningful benzamides[13] **4** were smoothly converted into isoquinolones **5** under otherwise identical reaction conditions (Scheme 3).

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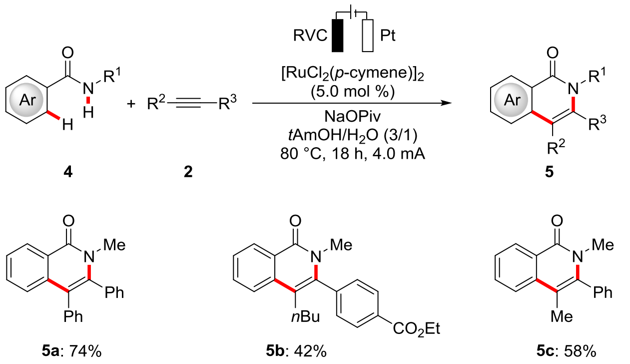
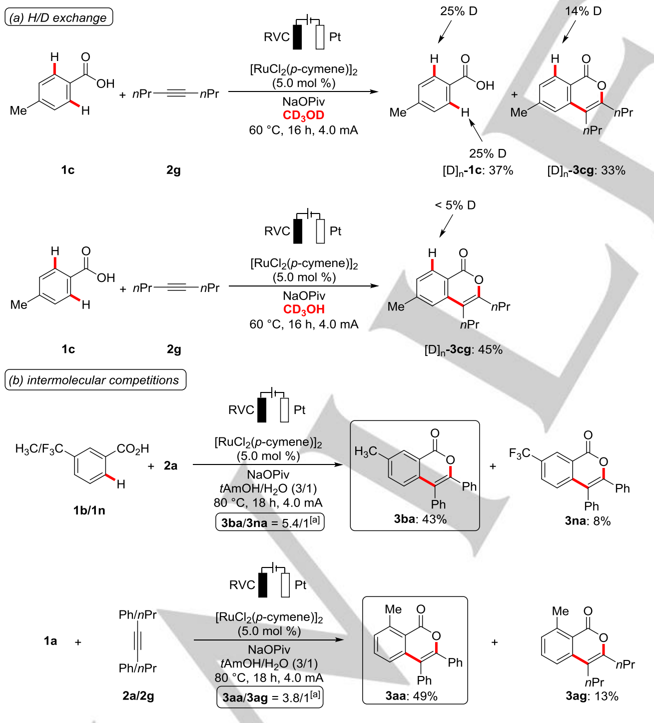


Scheme 3. Electrochemical C–H/N–H annulation by benzamides **4**.

In consideration of the unique efficacy of the electrochemical ruthenium-catalyzed C–H activation by weak coordination, we became attracted to delineating the catalyst's working mode. To this end, reactions with isotopically labelled solvents CD_3OD and CD_3OH were suggestive of a reversible C–H cleavage, occurring by organometallic C–Ru formation (Scheme 4a). Moreover, intermolecular competition experiments provided strong support for electron-rich arenes **1** and arylalkynes **2** to inherently react preferentially (Scheme 4b)



Scheme 4. Mechanistic studies on electrochemical C–H activation by weak *O*-coordination. [a] by GC/MS analysis with *n*-dodecane as internal standard.

Finally, we probed the electrochemical C–H activation by means of cyclovoltammetric analysis. Here, we focused on the key oxidation of the ruthenium(0) intermediate **6** by electricity (Figure 2). Thus, we observed a significant influence of the oxidation potential on the presence of acid ranging from 0.64-0.52 V *vs* Fc/Fc^+, indicating a strong beneficial effect of pivalic acid on the anodic oxidation of the ruthenium(0) intermediates **6**. In sharp contrast, the presence of base resulted in a considerably higher potential of up to 0.70 V (Figure S-1 in the SI).[10]

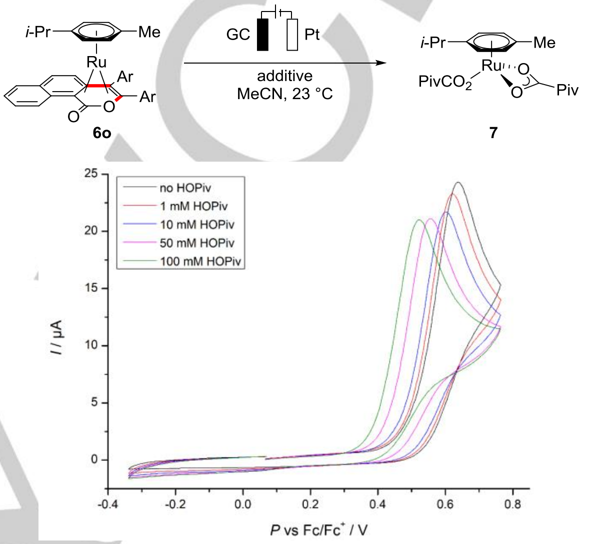
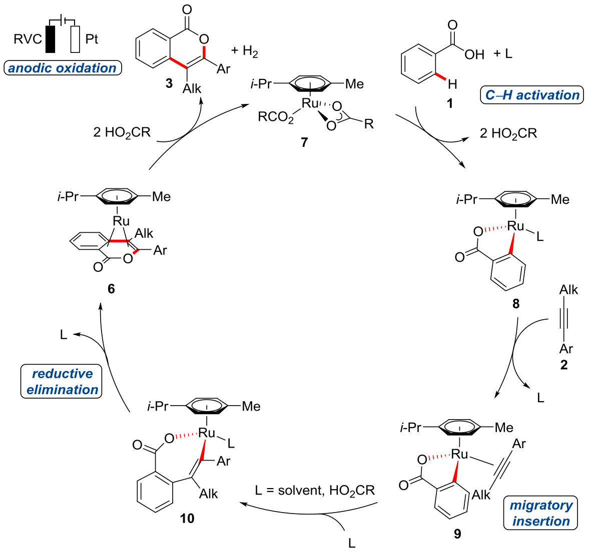


Figure 2. Cyclic voltammograms of **6o** (1 mM) in MeCN at 100 mV/s with nBu_4NPF_6 (0.1 M) as electrolyte in the absence (black) or presence of HOPiv. Ar = 4-$(F_3C)C_6H_4$. GC = glassy carbon electrode.

Based on our mechanistic studies, we propose a plausible catalytic cycle to commence by facile organometallic C–H activation (Scheme 5). Thereby, ruthena(II)cycle **8** is generated,[11; 14] along with two equivalents of carboxylic acid. Thereafter, migratory alkyne insertion furnishes the seven-membered ruthena(II)cycle **10**,[15] which rapidly undergoes reductive elimination to deliver the ruthenium(0) sandwich complex **6**. The key reoxidation of the ruthenium(0) complex is finally accomplished by anodic oxidation.



Scheme 5. Proposed catalytic cycle.

In conclusion, we have reported on the first electrocatalytic organometallic C–H activation with weakly *O*-coordinating groups. Thus, a versatile ruthenium(II) carboxylate catalyst enabled C–H/O–H alkyne annulations by synthetically meaningful benzoic acids with ample scope. The C–H activation employed electricity as the only oxidant and generated hydrogen as the sole byproduct. Mechanistic studies provided strong support for a fast organometallic C–H ruthenation and an efficient electrooxidation of the key ruthenium(0) intermediate by environmentally-benign electricity.

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Keywords: C–H activation • alkyne annulation • electrochemistry • electrocatalysis • mechanism • ruthenium

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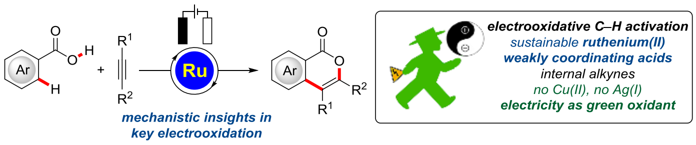
COMMUNICATION

*Youai Qiu, Cong Tian, Leonardo Massignan, Torben Rogge, and Lutz Ackermann**

Page No. – Page No.

Electrooxidative Ruthenium-Catalyzed C–H/O–H Annulation by Weak *O*-Coordination



Weak-electro: A versatile ruthenium(II) catalyst enabled electrooxidative C–H/Het–H activations by weak coordination with electricity as sustainable oxidant.