

Metallaelectro-Catalyzed C–H Activation by Weak Coordination

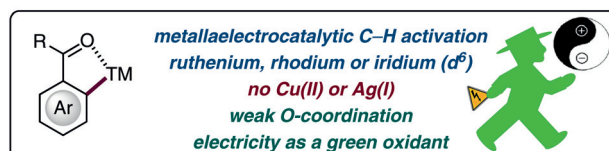
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Abstract The merger of organometallic C–H activation with electrocatalysis has emerged as a powerful strategy for molecular synthesis, avoiding the use of toxic and expensive chemical oxidants in stoichiometric quantities. This review summarizes recent progress in transition-metal-catalyzed electrochemical C–H activation by weak chelation assistance until March 2019.

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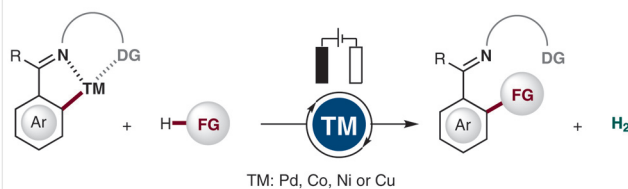
Key words electrochemistry, C–H activation, metallaelectro-catalysis, transition metals, weak O-coordination

1 Introduction

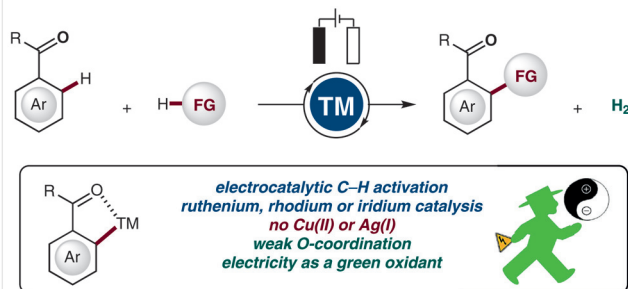
Organic electrosynthesis has been identified as an increasingly powerful tool in molecular sciences,¹ with transformative power for replacing stoichiometric chemical redox reagents. Based on key contributions by Baran,² Waldvogel,³ Ackermann,⁴ Yoshida,⁵ Xu⁶ and Lei among others,⁷ this strategy has recently proven feasible for establishing alkene difunctionalizations,⁸ direct oxygenations,⁹ oxidative and reductive couplings,¹⁰ polymerizations¹¹ and C–C activation,¹² as well as C–H activation¹³ with palladium,¹⁴ cobalt,¹⁵ ruthenium,¹⁶ rhodium,¹⁷ iridium,¹⁸ nickel¹⁹ and copper²⁰ complexes.⁴ Despite these indisputable advances, palladium, cobalt, nickel and copper catalysis continue to be severely limited to substrates bearing nitrogen-contain-

ing, strongly coordinating directing groups (Scheme 1a), prominently featuring arylpyridines. In sharp contrast, rhodium,¹⁷ ruthenium¹⁶ and iridium¹⁸ catalysts with d^6 -electron configuration have very recently allowed for the electrooxidative C–H activation with significantly more challenging, weakly coordinating, oxygen-containing substrates,²¹ setting the stage for versatile C–H functionalizations with synthetically meaningful acids and alcohols.²² This article highlights these recent advances in electrochemical, weak O-assisted C–H activations until March 2019 (Scheme 1b).

a) Previous work: metallaelectrochemical C–H activation by **strong N-coordination**



b) This review: metallaelectrochemical C–H activation by **weak O-coordination**



Scheme 1 Metallaelectro-catalyzed C–H activation

2 Ruthenaelectro-Catalyzed C–H Activation

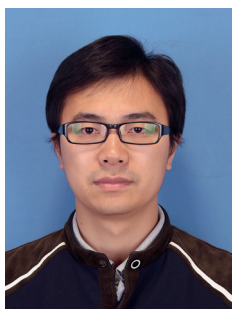
Ruthenium catalysts feature unique chemo- and site-selectivities within sustainable C–H activations.²³ Recently, the Ackermann group devised the first transition-metal-catalyzed electrocatalytic C–H activation by oxygen-based chelation assistance (Scheme 2).^{16c} Thus, a ruthenium(II) carboxylate catalyst enabled the electrooxidative C–H/O–H functionalization for alkyne annulations in the absence of chemical sacrificial oxidants. The ruthenium-catalyzed electrooxidative C–H activation was characterized by high catalytic efficacy and good functional group tolerance, including sensitive chlorides, bromides, esters and nitriles. In contrast to palladium catalysis, the ruthenaelectro-catalysis could conveniently be conducted in a most user-friendly undivided cell set-up. The electrooxidative annulation of

unsymmetrical alkynes **2i** and **2j** occurred with high levels of regiocontrol, placing the aromatic motif proximal to the oxygen in products **3ai** and **3aj**.

Based on cyclic voltammetry and electrolysis of the pre-formed ruthenium(0) intermediate **4**, a considerable beneficial effect of pivalic acid on the anodic oxidation of the ruthenium(0) intermediate **4** was observed (Scheme 3).^{16c} Furthermore, mechanistic studies provided strong support for a facile organometallic C–H ruthenation and electrochemical reoxidation of the key ruthenium(0) intermediate **4**.

Based on these studies, a possible catalytic cycle was proposed, which commences with the five-membered ruthena(II)cycle **7** by facile base-assisted internal electrophilic-type substitution (BIES)²⁴ C–H metalation (Scheme 4).^{16c} Thereafter, migratory insertion occurs to furnish the seven-membered ruthena(II)cycle **9**, while subsequent reductive

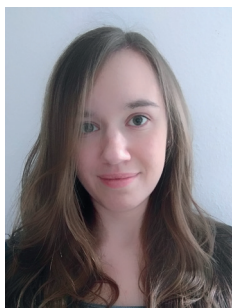
Biographical Sketches



Youai Qiu grew up in Jiangsu Province, China. He received his B.S. degree from China University of Mining and Technology (2007), and his Ph.D. from Zhejiang University (2015) under

the supervision of Prof. Shengming Ma. After postdoctoral work with Prof. Jan-Erling Bäckvall at Stockholm University, he joined Prof. Lutz Ackermann's group at Göttingen University in

September 2017. His current research interests focus on transition-metal-catalyzed transformations and synthetic electrocatalysis.



Julia Struwe obtained her B.S. and M.S. degrees from Georg-August-Universität Göttingen, Germany, where she is pursuing

her Ph.D. under the guidance of Prof. Lutz Ackermann. Her current research involves the development of sustainable and

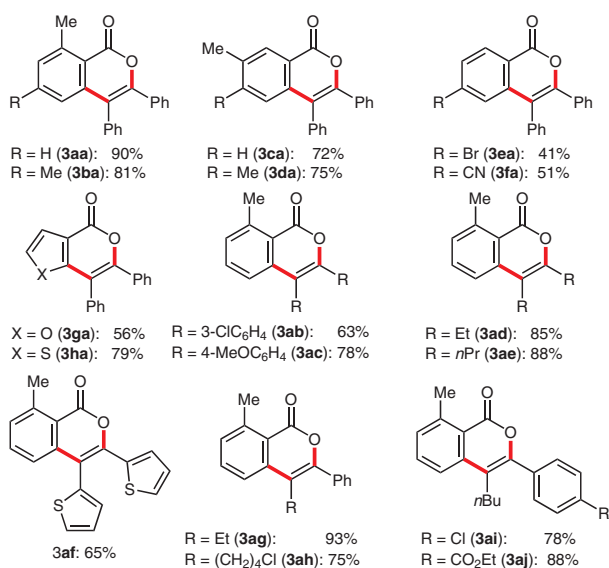
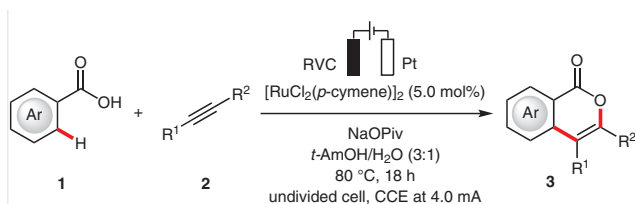
electrochemical procedures for C–H activation.



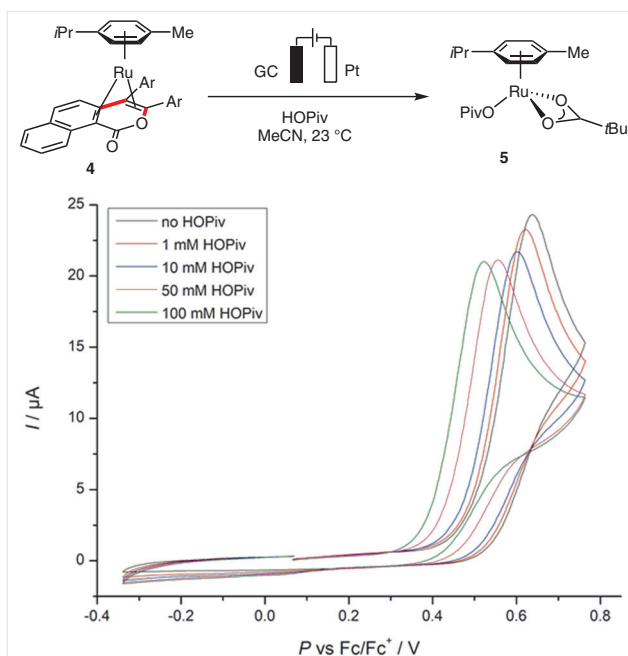
Lutz Ackermann studied chemistry at Kiel University (Germany), and undertook his Ph.D. with Prof. Alois Fürstner at the Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, 2001). After a postdoctoral stay at the University of California, Berkeley with Prof.

Robert G. Bergman, he initiated his independent research career in 2003 at the Ludwig-Maximilians-Universität München. In 2007, he became a Full Professor (W3) at Georg-August-Universität Göttingen. His recent awards and distinctions include an AstraZeneca Excellence in

Chemistry Award (2011), an ERC Grant (2012) and a Gottfried Wilhelm Leibniz-Preis (2017). The development and application of novel concepts for sustainable catalysis constitutes his major current research interests, with a topical focus on C–H activation.

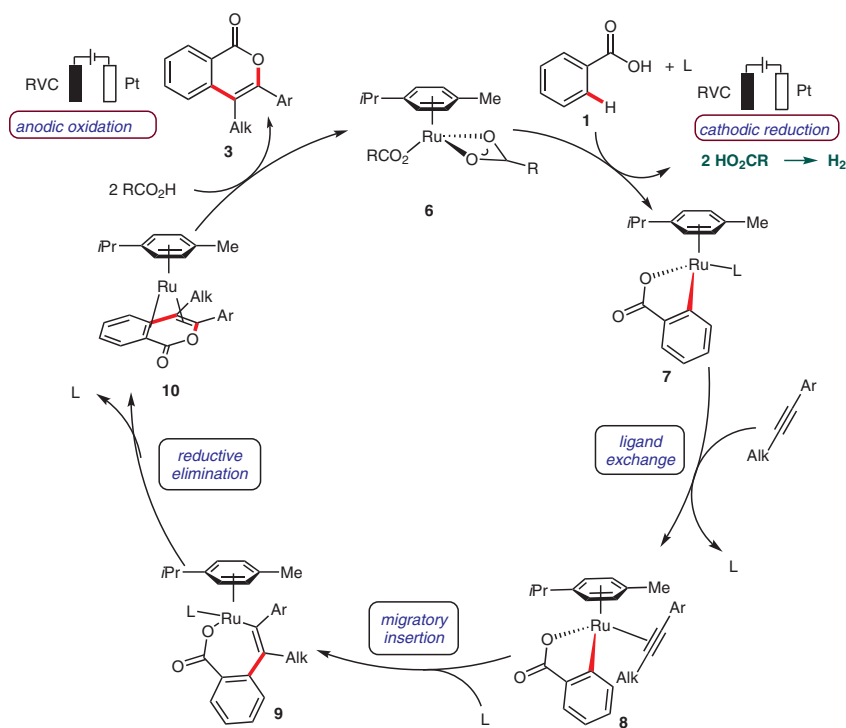


Scheme 2 Ruthenalectro-catalyzed C-H/O-H functionalization



Scheme 3 CV studies of ruthenalectro-catalyzed reoxidation

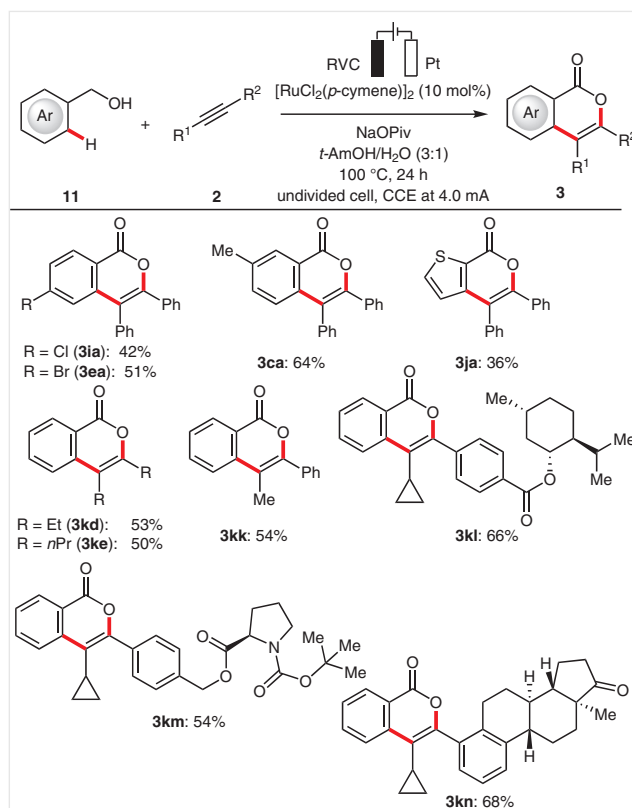
elimination delivers the ruthenium(0) sandwich complex **10**. Finally, the key anodic oxidation of ruthenium(0) intermediate **10** regenerates the catalytically active complex **6**, while liberating the desired product **3**.



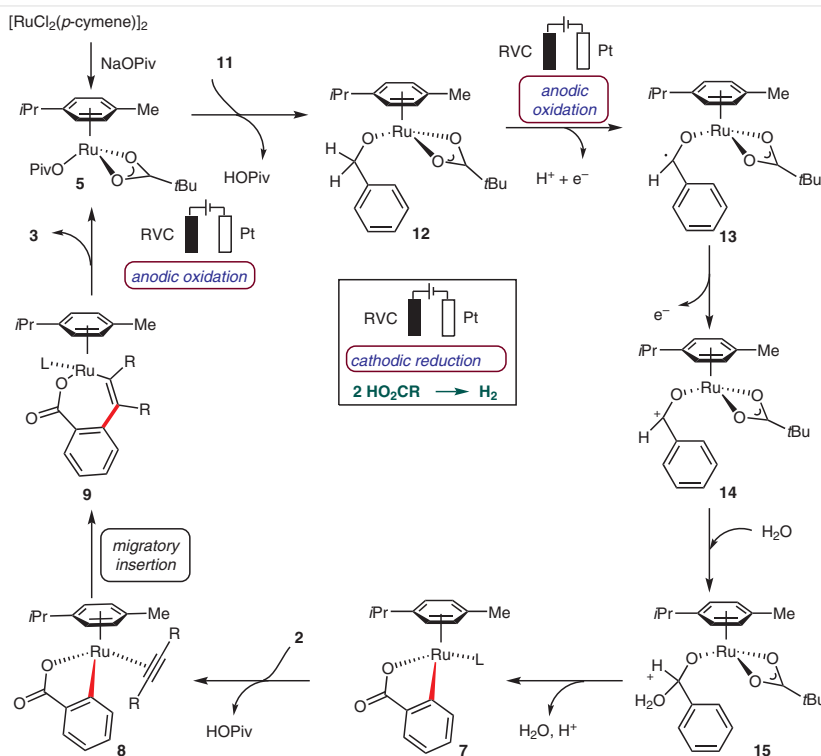
Scheme 4 A plausible mechanism for the ruthenalectro-catalyzed C-H/O-H annulation

Based on Ackermann's strategy, Li's group reported the ruthenium(II)-catalyzed electrooxidative [4+2] annulation of primary benzylic alcohols **11** with internal alkynes **2**, which allowed for benzylic alcohols as weakly *O*-directing-group precursors to access isocoumarins **3** via multiple C–H functionalization (Scheme 5).^{16a} The reaction proceeded with ample scope, tolerated a wide range of functional groups and incorporated the isocoumarin motif into diverse bioactive molecules in a step-economical manner.

Based on mechanistic studies and CV analysis, a plausible catalytic cycle was elaborated, as depicted in Scheme 6, including anodic single-electron oxidation of the intermediate **12**.^{16a} Thereafter, electron transfer forms the cationic intermediate **14**, which sequentially undergoes nucleophilic attack by water, while oxidation affords the organometallic ruthenium(II) intermediate **7**. Subsequent migratory insertion of the alkyne **2** forms the seven-membered ruthena(II)cycle **9**. Finally, reductive elimination delivers the desired product **3** and generates the ruthenium(0) complex.

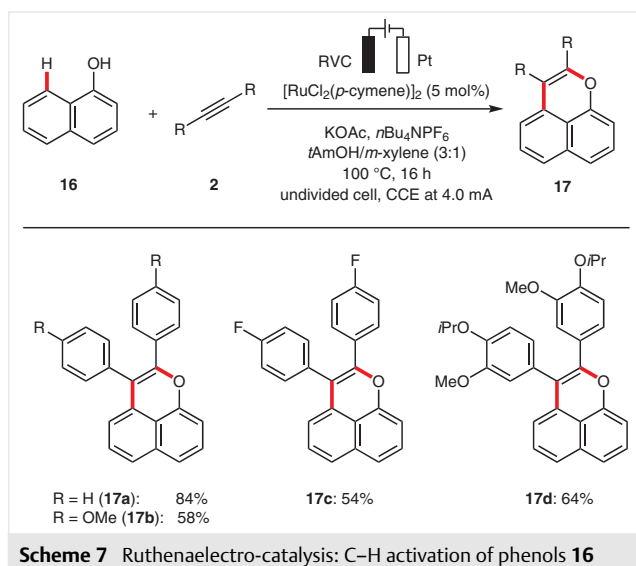


Scheme 5 Ruthenaelectro-catalyzed electrochemical C–H activation of benzylic alcohols **11**



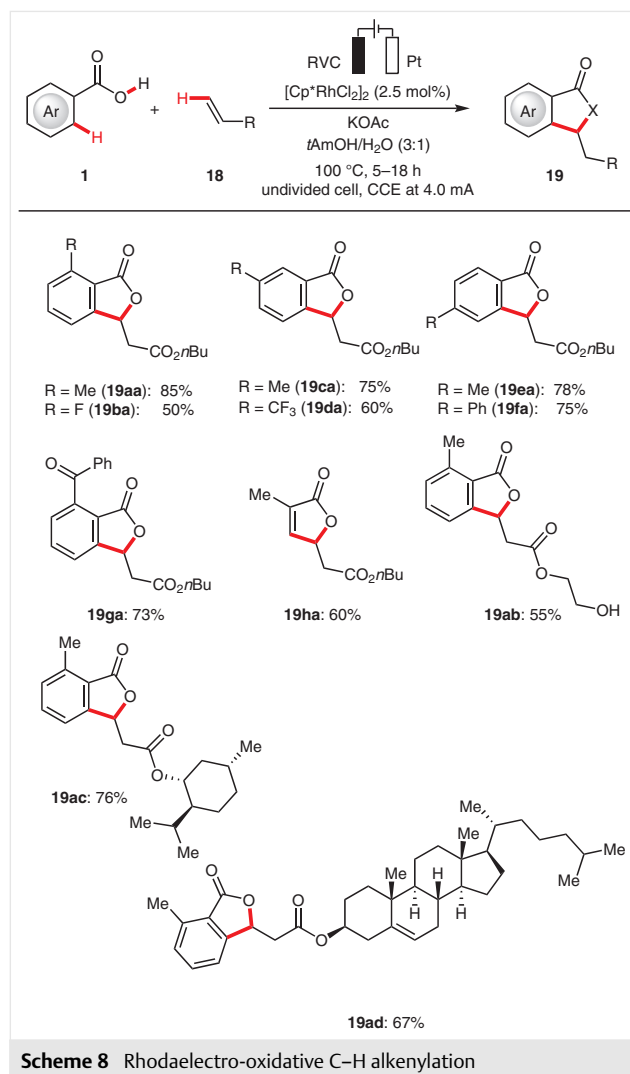
Scheme 6 Proposed catalytic cycle for ruthenaelectro-catalyzed C–H/O–H functionalization

Furthermore, Ackermann reported on the electrocatalytic organometallic C–H activation with challenging, weakly coordinating phenols **16** (Scheme 7).^{16d} Hence, a versatile ruthenium(II) carboxylate catalyst allowed for the electrooxidative C–H/O–H activation/alkyne annulations with ample scope. The strategy proved to be highly effective for the annulation of alkynes **2** by weakly coordinating naphthol derivatives **16**. The C–H activation employed electricity as the sole oxidant, while generating molecular hydrogen as the only byproduct. Mechanistic studies revealed an organometallic C–H ruthenation, along with an efficient electro-reoxidation of the key ruthenium(0) intermediate by environmentally benign electricity as a renewable energy source.

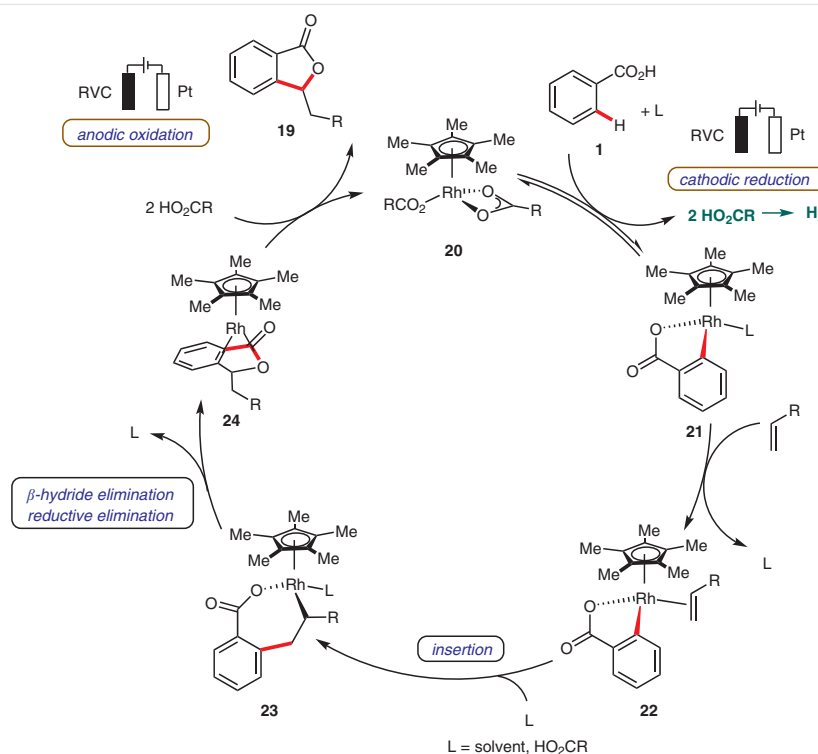


3 Rhodaelectro-Catalyzed C–H Activation

Rhodium(III) catalysis has proven particularly instrumental for a wealth of oxidative C–H functionalizations and heterocycle syntheses.²⁵ Despite major advances, these transformations had typically relied on stoichiometric amounts of toxic and expensive sacrificial metal oxidants, such as copper(II) or silver(I) salts. Very recently, Ackermann realized the unprecedented electrochemical, rhodium-catalyzed, twofold C–H/C–H alkenylation, using weakly *O*-coordinating benzoic acids **1** (Scheme 8).¹⁷ Valuable electrophilic functional groups were fully tolerated, including sensitive ketones and esters. It is noteworthy that more sterically hindered substituents at the *ortho*-position of benzoic acids **1** were also accepted. Acrylates **18** bearing free hydroxy or steroid functional groups likewise furnished the corresponding products efficiently. The rhodaelectro-catalyzed C–H activation was not limited to arenes **1**. Indeed, synthetically meaningful alkenes proved to be amenable as well, as illustrated with lactone **19ha**.



Based on comprehensive experimental mechanistic studies aligned with detailed computation, a plausible catalytic cycle was put forward (Scheme 9). After formation of the rhodium bis-carboxylate complex **20**, the catalytic cycle commences via facile C–H activation by carboxylate assistance. Coordination of the alkene, along with olefin insertion, leads to formation of the seven-membered rhodacycle **23**. Subsequent β -hydride elimination and reductive elimination forms rhodium(I) sandwich complex **24**. Finally, ligand exchange and anodic oxidation of the metal center in intermediate **24** liberates the desired phthalide product **19** and regenerates the active catalyst. The sole byproduct of this sustainable, environmentally benign reaction is molecular hydrogen, formed via cathodic reduction, as was evidenced by careful headspace GC analysis.



Scheme 9 Rhodaelectro-catalyzed C–H alkenylation: Mechanism

4 Iridaelectro-catalyzed C–H Activation

Besides ruthenium and rhodium catalysts, iridium complexes have also been recognized as powerful tools in C–H functionalization technology.²⁶ While this research area was largely dominated by chemical oxidants, Ackermann realized the first electrooxidative iridium-catalyzed C–H activation through weak *O*-coordination (Scheme 10).¹⁸ These C–H transformations featured a high functional-group tolerance with the aid of the metal-free redox mediator *p*-benzoquinone (BQ) through indirect electrolysis. It is noteworthy, that sensitive electrophilic groups, such as cyano, ester, chloro, bromo and even reactive iodo substituents were fully tolerated. The unique robustness of the synergistic iridium electro-catalyzed C–H activation allowed for the efficient use of acrylamide, a steroid and peptides.

The synergistic iridaelectro-catalysis was mirrored by the chemoselective C–H activation of sensitive halogenated arenes, clearly outcompeting rhodium(III) catalysts (Scheme 11). These findings emphasize the outstanding performance and selectivity profile through the redox-catalyst-enabled indirect iridium electrocatalysis.

To explore the working mode of the catalyst, mechanistic studies were performed. To this end, deuterium labeling, intermolecular competition experiments and KIE studies were rationalized by facile C–H bond cleavage in terms of a BIES²⁴ manifold. In addition, the role of benzoquinone as a

redox mediator was investigated by cyclic voltammetry studies (Figure 1).²⁷ The disappearance of the back-scan peak and the iridium redox couple indicates an electron transfer from benzoquinone to the metal center of the catalyst.

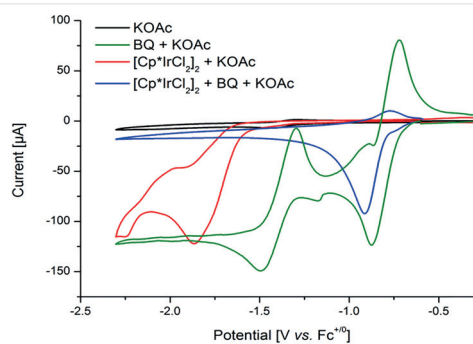
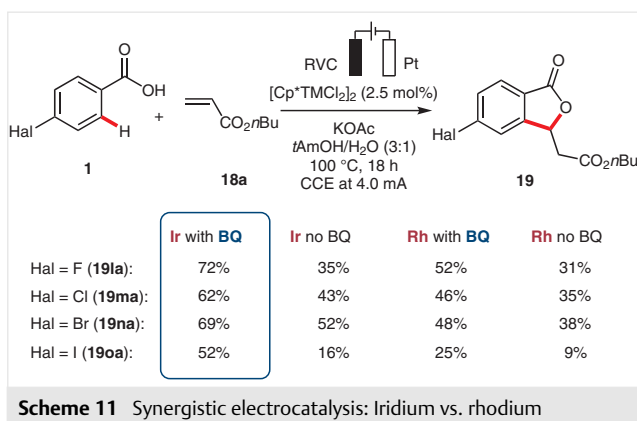
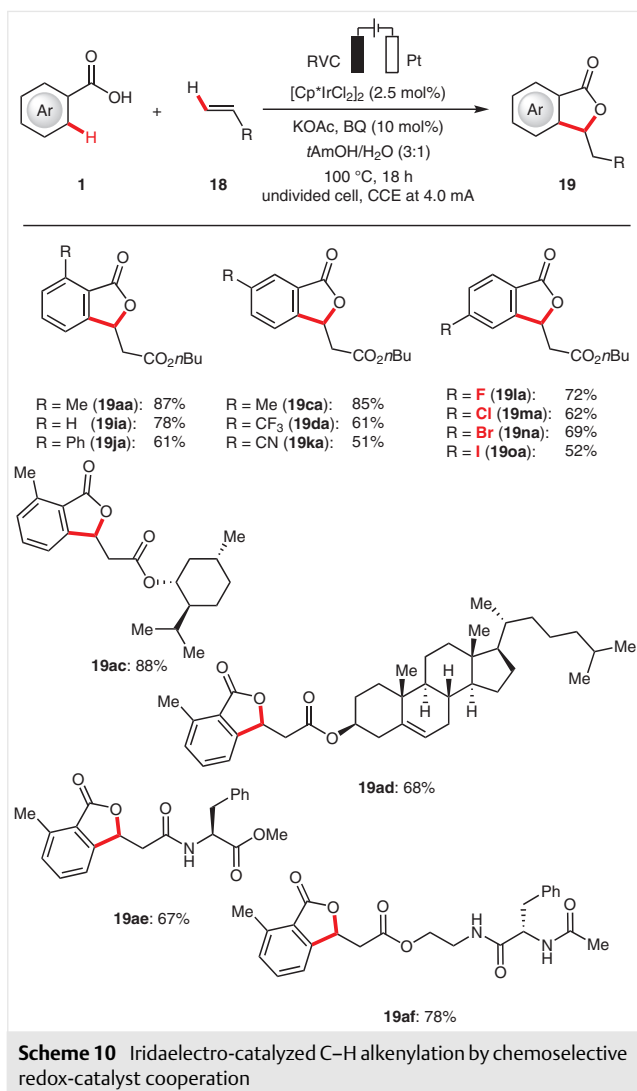


Figure 1 CV studies on electrochemical iridaelectro-catalyzed C–H alkenylation

Based on detailed mechanistic studies, a plausible catalytic cycle was proposed for the synergistic electrochemical iridium-catalyzed C–H alkenylation (Scheme 12). The catalytic cycle commences by a facile organometallic C–H activation. Next, migratory alkene insertion occurs to form seven-membered iridium cycle **28**. Thereafter, β -hydride elimination and reductive elimination furnishes the key



iridium(I) sandwich complex **29**, which is reoxidized by *p*-benzoquinone (**30**) and regenerates the catalytically active complex. Finally, hydroquinone (**31**) undergoes anodic oxidation to form *p*-benzoquinone.

5 Summary and Outlook

In recent years, metallaelectro-catalyzed C-H activation has emerged as an increasingly powerful tool for sustainable organic synthesis, which employs renewable²⁸ electricity as the sole oxidant. Thus, sustainable metallaelectro-catalysis avoids the use of stoichiometric amounts of sacrificial chemical oxidants. Numerous elegant transformations have been developed involving electrochemical transition-metal-catalyzed C-H functionalizations, prominently featuring palladium catalysis. Despite significant advances in the field, palladium, but also cobalt, copper and nickel catalysts were thus far severely restricted to strongly coordinating, nitrogen-containing directing groups. Very recently, this major limitation in metallaelectro-catalysis was successfully addressed by means of ruthenium(II), rhodium(III) and iridium(III) catalysis, setting the stage for challenging C-H activations with weakly *O*-coordinating acids and alcohols. Thus, transition metals with d⁶-electron configuration enabled metallaelectro-catalysis being devoid of nitrogen-containing directing groups. In addition to the d⁶-electron configuration, the stabilization of the transition metals by arene or cyclopentadienyl ligands proved to be beneficial so as to avoid cathodic reduction under undivided cell conditions. Hence, ruthenium(II)bis(carboxylate) catalysts²⁹ proved broadly applicable to benzoic acids, acrylic acids and phenols, even involving multiple C-H functionalizations. In contrast, iridium-catalyzed electrochemistry strongly benefited from assistance by a cooperative redox mediator, resulting in broad substrate scope and excellent tolerance of sensitive functional groups, including reactive iodoarenes. Given the sustainable nature of electrochemical C-H activation, exciting future advances are to be expected in this rapidly evolving research area, which should among others address electro-flow approaches, enantioselective metallaelectro-catalysis and photoelectrochemical C-H functionalizations.

Funding Information

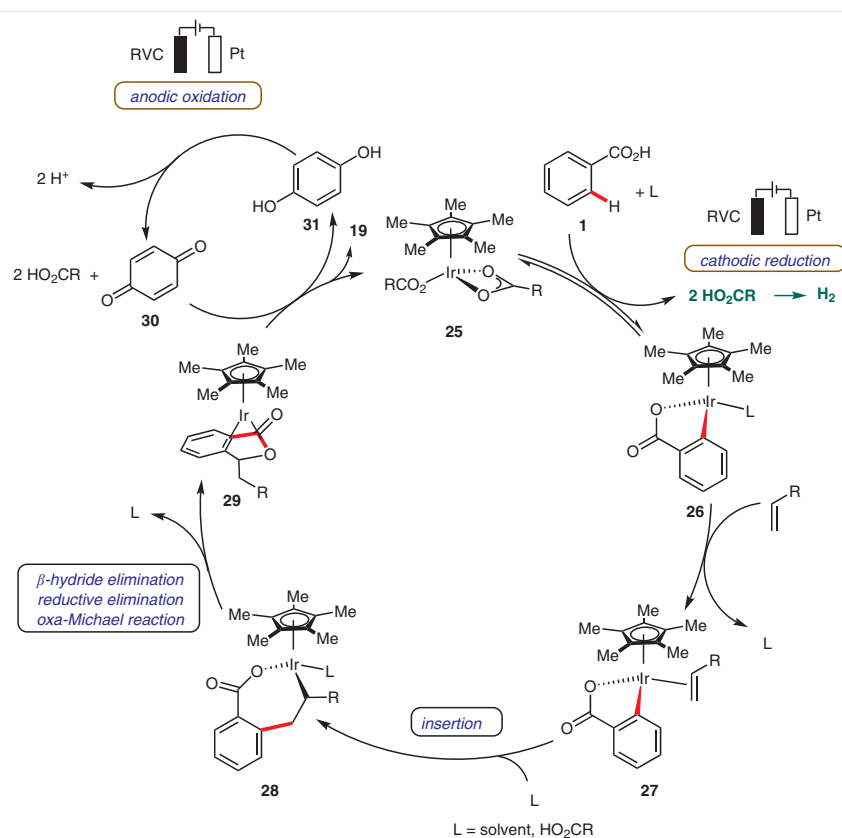
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Scheme 12 Iridaelectro-catalyzed C–H alkenylation: Proposed catalytic cycle

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