Chinese Chemical Letters 35 (2024) 109916

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Editorial

Sustainable electrosynthesis: Enantioselective electrochemical Rh(III)/chiral carboxylic acid-catalyzed oxidative C–H cyclization coupled with hydrogen evolution reaction

Chiral compounds play a crucial role in the development of pharmaceuticals, pesticides, fragrances, and materials due to their unique stereochemical configurations. Asymmetric catalysis, which employs chiral catalysts to favor the production of one enantiomer over its mirror image, has emerged as a pivotal technique in the synthesis of chiral compounds [1]. However, traditional asymmetric methods sometimes rely on environmentally harmful reducing or oxidizing agents, presenting a considerable challenge in the pursuit of green chemistry.

In response to this challenge, recent research has been directed towards the development of sustainable catalytic techniques, which strive to reduce or eliminate the use of hazardous substances. Among these advancements, organic electrosynthesis has garnered notable attention. This strategy employs electricity, a inexpensive and readily available resource, as a substitute for traditional noxious oxidizing and reducing agents in redox reactions. The integration of electrochemical strategies into asymmetric synthesis represents a significant advancement towards sustainable and environmentally friendly asymmetric catalysis processes [2].

A leading approach in electrochemical asymmetric synthesis is the transition metal-catalyzed strategy, particularly exemplified by enantioselective electrochemical Rh(III)-catalyzed oxidative C–H activation. Rhodium's versatile and adjustable valence states empower unparalleled chemical, regioselective, and enantioselective mastery over the reaction processes. Within the scope of Rh(III)-catalyzed enantioselective electrochemical oxidative C–H activation, two catalysts: Chiral cyclopentadienylrhodium [Cp^{x}Rh(III)] and achiral cyclopentadienylrhodium/chiral carboxylic acid [Cp*Rh(III)/(CCA)], have emerged as successful asymmetric C–H functionalization activity. Chiral Cp^{x}Rh(III) catalysts exhibit exceptional performance in both redox-neutral and oxidative C–H activation reactions, benefiting from the unique mechanisms offered by electrochemical processes.

For instance, Mei and colleagues demonstrated an enantioselective electrochemical Rh-catalyzed synthesis of spiropyrazolones through C–H annulation with alkynes in an undivided cell (Fig. 1) [3]. This reaction protocol could afford a variety of chiral spiropyrazolones with good yields and enantioselectivities (up to 92% yield and 95:5 *er*). They demonstrated that oxidation-induced reductive elimination was essential, and the Rh(III) catalyst was regenerated through anodic oxidation.

Compared to chiral CpxRh(III) catalysts, Cp*Rh(III)/CCA catalysts pose several challenges in electrochemical reactions. Specifically, CCA tends to undergo electrochemical side reactions, such as the Kolbe reaction or lactonization [4]. Additionally, competitive Rh-catalyzed C–H acyloxylation with CCA may occur under electrolytic conditions, which undermines the efficiency of the desired reaction pathway [5]. Furthermore, the stereochemistry control of the products, which is a crucial aspect of asymmetric synthesis, is compromised. This may be due to the incompatibility of ligands with the electrolyte solution used in the reaction. These challenges emphasize the need for further improvement in the use of Cp*Rh(III)/CCA catalysts under electrochemical conditions.

Recently, Shi and Zhou *et al.* reported the first achiral Cp*Rh(III)/spiroCCA-catalyzed electrochemical enantioselective C–H annulation of sulfoximines with alkynes in an undivided cell (Fig. 2) [6]. The electrochemical conditions tolerated diarylacetylenes bearing various electron-donating and electron-withdrawing groups. As a result, a variety of enantioenriched 1,2-benzothiazines were obtained in moderate to good yields with excellent enantioselectivities (up to 99% yield and 98:2 *er*). The presence of Et_3N significantly improved the enantioselectivity of the reaction. This improvement may be attributed to the assistance of Et_3N in the C–H activation step.

During mechanistic investigations, the synthesis and transformation of Rh(III)-Int complex revealed that Rh(III)-Int was likely a pivotal catalytic intermediate, indicating the participation of a Rh(III)/Rh(I) catalytic cycle in this protocol. Based on these studies, a plausible catalytic mechanism was proposed (Fig. 3). Initially, enantioselective C–H cleavage occurs through the collaboration of the Cp*Rh(III) catalyst **A**, chiral carboxylic acid (CCA) and the sulfoximine, yielding the Rh(III)-Int **B**. Subsequent ligand exchange with an alkyne leads to intermediate **C**, which then undergoes migratory insertion of the alkyne to form the seven-membered complex **D**. Reductive elimination of **D** results in the Rh(I)-Int **E**. Ultimately, anodic oxidation facilitates the formation of the desired product **3** from **E**, while concurrently regenerating the Rh(III) catalyst **A**. Correspondingly, protons are reduced on the cathode to generate H_2.

The robustness of this strategy was tested using 95% industrial-grade ethanol as a solvent, resulting in a 93% yield and a 95:5 ratio of corresponding 1,2-benzothiazine. Subsequently, a user-friendly batch reactor with external circulation was developed for large-

https://doi.org/10.1016/j.cclet.2024.109916

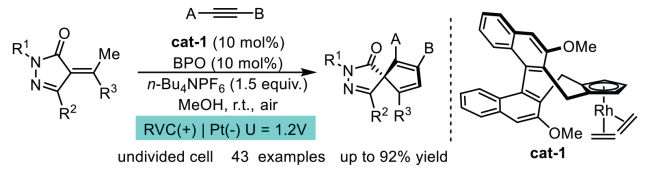

Fig. 1. Enantioselective electrochemical Cp^{x}Rh(III)-catalyzed synthesis of spiropyrazolones.

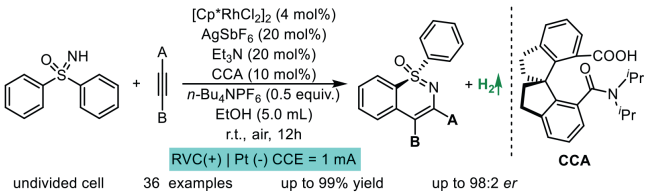

Fig. 2. Enantioselective electrochemical Cp*Rh(III)/CCA-catalyzed synthesis of 1,2-benzothiazines.

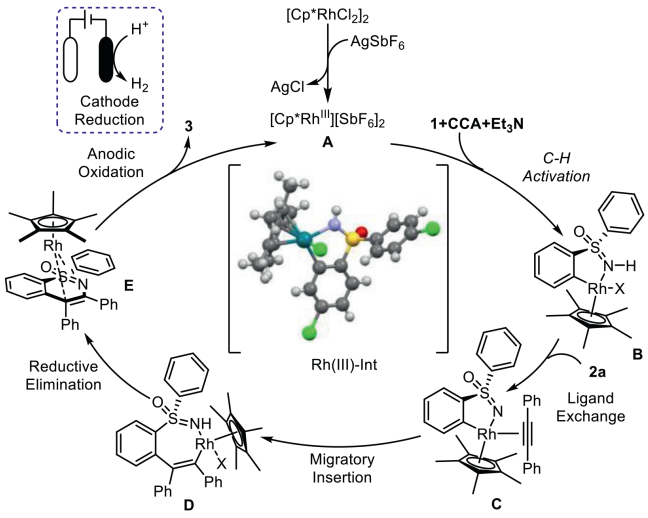

Fig. 3. Mechanism of the enantioselective electrochemical Cp*Rh(III)/CCA-catalyzed synthesis of 1,2-benzothiazines.

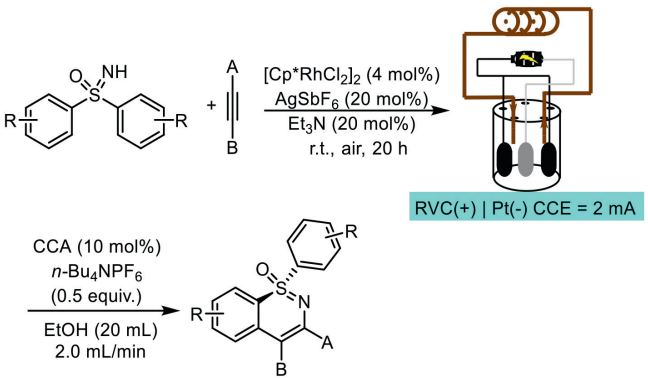

Fig. 4. Applications of the Enantioselective electrochemical Cp*Rh(III)/CCA-catalyzed synthesis of 1,2-benzothiazines.

scale synthesis (Fig. 4). Several substrates efficiently yielded the desired product with good yields (up to 78%) and high enantioselectivities (up to 98:2 *er*). This innovative device significantly simplifies the scaling up of electrochemical organic synthesis reactions.

Moreover, Shi and Zhou *et al.* developed the first enantioselective electrochemical Rh(III)-catalyzed sulfoximine C–H/N–H cyclization reaction by using achiral Cp*Rh(III) and commercially available chiral carboxylic acids (CCA) as catalyst to obtain a series of enantioenriched 1,2-benzothiazines in moderate to good yields with excellent enantioselectivities. In the mechanistic study, the preparation, isolation, and conversion of reaction key intermediate were achieved. This reaction is easy to operate and can be scaled up using an innovative external-cycle batch reactor.

It was observed that during rhodium-catalyzed asymmetric synthesis at the anode, H_2 is produced as a by-product in the cathode, which is consistent with the strategy of transition-metal-catalyzed electrochemical C–H activation with hydrogen evolution reaction (HER) [7]. This strategy has gained significant attention for its adherence to green and sustainable chemistry principles. Compared to research on reactions catalyzed by ruthenium [8], rhodium, and palladium [9], those involving abundant metals are receiving increasing attention.

Recently, Guo's group revealed a synergistic Ni/Cu dual-catalyzed stereodivergent electrooxidative C(sp^3)-H/C(sp^3)-H homocoupling of racemic benzoxazolyl acetate with abroad scope, uniformly good yield, high diastereoselectivity, and excellent enantioselectivity (Fig. 5) [10].

Shi group reported the first electrooxidative cobalt-catalyzed enantio– and regioselective C–H/N–H annulation with olefins through a mechanism-based ligand design strategy (Fig. 6) [11]. The strong cooperative effect between ^{t}Bu-Salox and 3,4,5-trichloropyridine enabled the highly enantio– and regioselective C–H annulation (up to 96% *ee* and 97:3 *rr*).

In the same year, Ackermann's group developed a cobalt-catalyzed electro-oxidative C–H and N–H annulation method, enabling the synthesis of C-stereogenic, atropoisomeric, and P-stereogenic chiral compounds with high enantiomeric ratios [12]. The use of natural sunlight as a power source greatly promoted the economy of this strategy, which represents a significant advancement in the field of sustainable asymmetric electrochemical synthesis (Fig. 7).

Enantioselective electrochemical reactions catalyzed by transition metals like rhodium, which couple hydrocarbon activation with hydrogen evolution, represent a recent advancement in green and sustainable chemistry. Currently, mechanistic studies of this reaction type primarily focus on carbon-hydrogen bond functionalization. Nevertheless, there is still a lack of understanding regarding the proton generation, transfer, and reduction process at the cathode during the reaction. This lack of understanding may limit the efficiency of hydrogen production. Further exploration of this class of reactions, particularly when integrated with electrochemical continuous flow reactors or external recirculation batch reactors, will significantly advance the green and sustainable synthesis of chemicals.

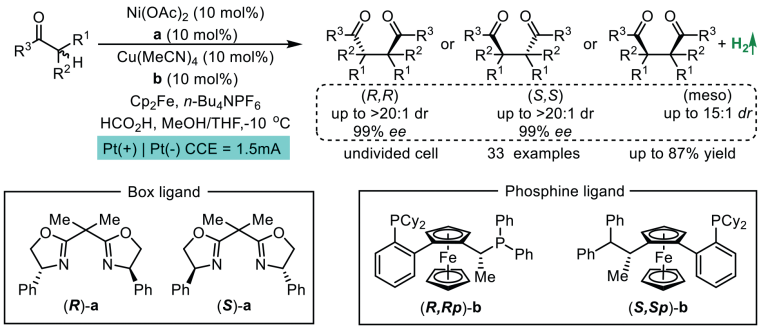

Fig. 5. Ni/Cu dual-catalyzed stereodivergent electrooxidative C(sp^3)-H/C(sp^3)-H homocoupling of racemic benzoxazolyl acetate.

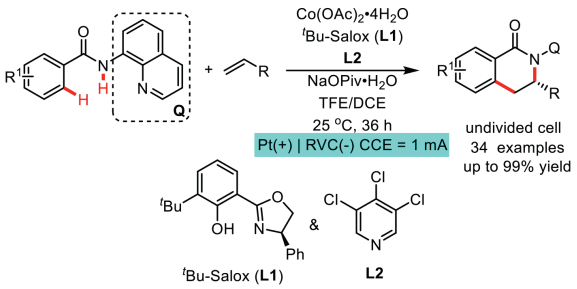

Fig. 6. Enantioselective electrochemical cobalt-catalyzed aryl C–H/N–H annulation.

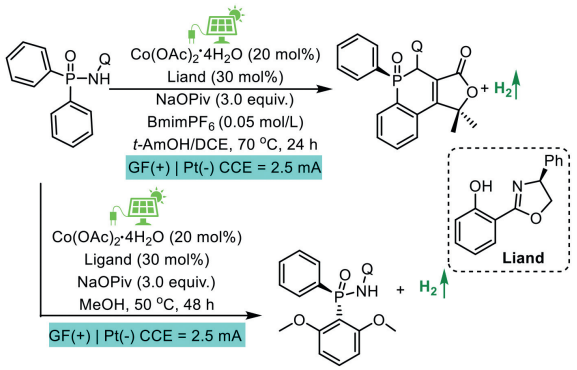

Fig. 7. Enantioselective electrochemical cobalt-catalyzed aryl C–H activation reactions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Xinghui Yao: Writing – original draft. **Zhouyu Wang:** Writing – review & editing. **Da-Gang Yu:** Writing – review & editing.

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Received 27 March 2024
Revised 15 April 2024
Accepted 21 April 2024
Available online 22 April 2024

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