Electrochemistry-Enabled Ir-Catalyzed Vinylic C–H Functionalization

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Synergistic use of electrochemistry and organometallic catalysis has emerged as a powerful tool for site-selective C–H functionalization, yet this type of transformation has thus far mainly been limited to arene C–H functionalization. Herein, we report the development of electrochemical vinylic C–H functionalization of acrylic acids with alkynes. In this reaction an iridium catalyst enables C–H/O–H functionalization for alkyne annulation, affording α -pyrones with good to excellent yields in an undivided cell. Preliminary mechanistic studies show that anodic oxidation is crucial for releasing the product and regeneration of a Ir(III) intermediate from a diene-Ir(I) complex, which is a coordinatively saturated, 18-electron complex. Importantly, common chemical oxidants such as Ag(I) or Cu(II) did not give significant amounts of the desired product in the absence of electrical current under otherwise identical conditions.

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Electrochemistry-Enabled Ir-Catalyzed Vinylic C–H Functionalization

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Supporting Information Placeholder

ABSTRACT Synergistic use of electrochemistry and organometallic catalysis has emerged as a powerful tool for site-selective C–H functionalization, yet this type of transformation has thus far mainly been limited to arene C–H functionalization. Herein, we report the development of electrochemical vinylic C–H functionalization of acrylic acids with alkynes. In this reaction an iridium catalyst enables C–H/O–H functionalization for alkyne annulation, affording α -pyrones with good to excellent yields in an undivided cell. Preliminary mechanistic studies show that anodic oxidation is crucial for releasing the product and regeneration of a Ir(III) intermediate from a diene-Ir(I) complex, which is a coordinatively saturated, 18-electron complex. Importantly, common chemical oxidants such as Ag(I) or Cu(II) did not give significant amounts of the desired product in the absence of electrical current under otherwise identical conditions.

The past decade has witnessed a renaissance in electrochemical organic synthesis. This approach utilizes electric current to replace conventional chemical oxidants or reductants to drive the reaction, thereby representing an environmentally friendly alternative to traditional approaches.¹ More importantly, in electrochemistry the potential can be precisely controlled, allowing for unique reactivity and chemoselectivity.² Among many electrochemical transformations, electrochemical C–H functionalization represents one of most promising reaction types, since this approach not only avoids prefunctionalization of the substrate but also provides novel disconnections in retrosynthetic analysis.³ Owing to the higher oxidation potentials of C–H bonds compared to common functional groups and organic solvents, mediated electrochemical oxidation is typically employed.⁴ For instance, Baran and co-worker recently elegantly developed a scalable and sustainable electrochemical allylic oxidation using tetrachloro-*N*-hydroxyphthalimide (Cl₄NHPI) as the mediator.⁵ The same group further demonstrated functionalizing non-activated C(sp³)-H bonds using quinuclidine as a redox mediator with moderate site-selectivity.⁶ In these cases,

Scheme 1. Electrochemical Vinylic C–H Functionalization

secondary or tertiary C–H bonds are preferentially functionalized over primary C–H bonds. Alternatively, our lab⁷ and the Sanford group⁸ independently developed site-selective electrochemical C(sp³)-H functionalization by merging with Pd catalysis, in which primary C–H bonds proximal to a suitable directing group are selectively functionalized.⁹ Similarly, metal-catalyzed site-selective electrochemical arene C–H functionalization was also developed with various metal catalysts, such as Pd,¹⁰ Ni,¹¹ Co,¹² Ru,¹³ Cu,¹⁴ Rh,¹⁵ and Ir.¹⁶ In these systems electric current was used as oxidant to turn over the catalyst.^{17,18} Electrochemical vinylic C–H functionalization, however, remains rare.¹⁹ Recently, Ackermann and co-workers reported an elegant Rh-catalyzed electrochemical C–H alkenylation of benzoic acids and benzamides, including two examples of vinylic C–H alkenylation.²⁰ General speaking, electrochemical oxidation of the alkene π -bond is much easier than functionalization a vinylic C–H bond, since the dissociation energy of the π -bond (about 65 kcal/mol) is much lower than that of the vinylic C–H bond (about 111

kcal/mol) (Scheme 1A).²¹ Herein, we report Ir-catalyzed electrochemical vinylic C–H annulation of acrylic acids with alkynes, affording various substituted α -pyrones (Scheme 1B), which are ubiquitous motifs found in many natural products and biological active small molecules (Scheme 1C).²² Although, vinylic C–H annulations of acrylic acids with alkynes to form α -pyrones were realized with Co,²³ Ru,²⁴ Rh,²⁵ and Pd catalysis,²⁶ the same transformation with Ir catalysis has not been realized to date,²⁷ presumably due to decarboxylation²⁸ or difficulty of dissociation of the Ir catalyst from the stable 18-electron diene-Ir(I) complex that is formed during the course of the reaction (Scheme 1B).²⁹

Table 1. Reaction Optimization with Substrate 1a^{a,b}

entry	variation from standard conditions ^a	yields(%) ^b
1	none	99(95) ^c
2	CH ₃ CN instead of MeOH	20
3	DMF instead of MeOH	23
4	CF ₃ CH ₂ OH instead of MeOH	44
5	HFIP instead of MeOH	43
6	3 mA instead of 1.5 mA (4 h)	90
7	6 mA instead of 1.5 mA (2 h)	83
8	40 °C instead of 60 °C	83
9	25 °C instead of 60 °C	72
10	KOAc instead of <i>n</i> -Bu ₄ NOAc	92
11	<i>n</i> -Bu ₄ NBF ₄ instead of <i>n</i> -Bu ₄ NOAc	<5
12	K ₂ CO ₃ instead of <i>n</i> -Bu ₄ NOAc	<5
13	O ₂ instead of electric current	<5
14	2 equiv Ag ₂ CO ₃ instead of electric current	<5
15	2 equiv Cu(OAc) ₂ instead of electric current	<5
16	2 equiv PhI(OAc) ₂ instead of electric current	18
17	no (Cp*IrCl ₂) ₂	nr
18	no electric current	nr

^aReaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), (Cp*IrCl₂)₂ (3 mol%), *n*-Bu₄NOAc (3.0 equiv) and MeOH (3 mL), in an undivided cell with two platinum electrodes (each 1.0 × 1.0 cm²), 60 °C, 1.5 mA, 12 h. ^bThe yield was determined by ¹H NMR using CH₂Br₂ as an internal standard. ^cIsolated yield in parentheses.

Initially, we chose 2-phenylacrylic acid (**1a**) and diphenylacetylene (**2a**) as model substrates and probed various reaction conditions in an undivided cell for the envisioned electrochemical vinylic C–H annulation (Table 1, and see Table S1–S5 in the Supporting Information). After extensive optimization, we found that 95% isolated yield of α -pyrone (**3a**) could be obtained under constant-current electrolysis at 1.5 mA in the presence of 3 mol% of (Cp*IrCl₂)₂, and three equivalents of *n*-Bu₄NOAc in MeOH at 60 °C after 12 h (Table 1, entry 1). The reactivity diminished significantly when other solvents were used (entries 2–5). Increasing electric current (entries 6 and 7) or decreasing the reaction temperature resulted in slightly lower yields (entries 8 and 9). Evaluating different electrolytes revealed that acetate anion is crucial for the reaction (entries 10–12).³⁰ It is worth noting that chemical oxidants, including O₂, Ag₂CO₃ and Cu(OAc)₂ did not give significant amounts of the desired product in the absence of electrical current under otherwise identical conditions (entry 13–15). However, 18% yield of **3a** was obtained when

PhI(OAc)₂ was employed (entry 16). This observation indicates that the merger of electrochemistry and iridium catalysis provides unique reactivity in this system. Finally, control experiments indicated that the Ir catalyst and electric current are both essential for this reaction (entries 17 and 18).

With the optimized reaction conditions in hand, the substrate scope was investigated to test the generality and identify limitations of this Ir-catalyzed electrochemical vinylic C–H annulation. As shown in Scheme 2, a variety of α -substituted acrylic acids all reacted well, affording the corresponding α -pyrones in good to excellent yields. Acrylic acids substituted with various of functional groups such as alkyl, ether, halides, trifluoromethyl, silyl, allyl, and ester groups were well tolerated under the standard conditions (**3a–3v**). The connectivities of **3b** and **3r** were unambiguously confirmed by X-ray analysis. Unsubstituted acrylic acid gave good yield (**3w**). In contrast, β -substituted acrylic acids generally gave lower yields (**3x–3z**).

Scheme 2. Evaluation of Acrylic Acid Scope^a

^aReaction conditions: **1a–1z** (0.24 mmol), **2a** (0.2 mmol), (Cp*IrCl₂)₂ (3 mol%), *n*-Bu₄NOAc (3.0 equiv) and MeOH (3 mL), in an undivided cell with two platinum electrodes (each 1.0 × 1.0 cm²), 60 °C, 1.5 mA, 12 h. ^bGram scale (6 mmol of **2a**).

Scheme 3. Evaluation of Alkyne Scope^a

^aReaction conditions: **1a** or **1l** (0.24 mmol), **4a-4r** or **5a-5s** (0.2 mmol), (Cp*IrCl₂)₂ (3 mol%), *n*-Bu₄NOAc (3.0 equiv) and MeOH (3 mL), in an undivided cell with two platinum electrodes (each 1.0 × 1.0 cm²), 60 °C, 1.5 mA, 12 h.

Next, we moved on to investigate the reactivity of a series of internal alkynes. As shown in Scheme 3, diarylacetylenes with various functional groups, such as alkyl, ether, halides, trifluoromethyl, cyano, and thiophene groups, were well tolerated, affording α -pyrones in good to excellent yields (**6a-6n**). In addition, dialkylacetylenes also resulted in good yields (**6o-6q**). To our delight, excellent regioselectivity was achieved with unsymmetrical alkynes, placing the aromatic moiety in proximal to the oxygen heteroatom (**7a-7o**). The structures of **6o**, **7g**, **7l** and **7m** were unambiguously verified by X-ray analysis. Furthermore, the developed protocol could be applied into the diversification of natural products, showcasing the potential utility of this chemistry (**7p-7s**).

To gain insight into the mechanism of this electrochemical vinylic C-H annulation, we first investigated the stoichio-

metric reaction of acrylic acids, alkynes, and (IrCp*Cl₂)₂ in the absence of electric current. Interestingly, in these cases the iridium sandwich complexes **8a-8f** could be obtained, with the corresponding α -pyrone serving as a neutral η^4 ligand. Their structures were unambiguously confirmed by X-ray analysis (Scheme 4). They are coordinatively saturated, 18-electron complexes, which explains their stability and inertness towards chemical oxidants (e.g., Ag(I) or Cu(II)). Next, complex **10** was synthesized by reacting IrCp*(OAc)₂(DMSO) complex **9** and substrate **1a** at 60 °C for 4 h, and its structure was verified by X-ray analysis (Scheme 5A). Complex **8a** was then obtained from by treating **10** with alkyne **2a**. Iridium complex **8a** found to be a competent intermediate and catalyst in electrochemical vinylic C-H annulation (Scheme 5B). Interestingly, treatment of **8a** with repre-

sentative chemical oxidants Ag_2CO_3 and $\text{Cu}(\text{OAc})_2$ at 60 °C or 120 °C did not give significant amounts of product **3a**. However, when **8a** was subjected to electric current, **3a** was formed in 84% yield (Scheme 5C). Complex **8a**, in a 0.1 M solution of *n*-Bu₄NPF₆ in MeCN exhibits oxidation peaks at 0.98 and 1.72 V versus SCE (curve a, Figure 1).³¹ This result indicates that **8a** is oxidized preferentially under anodic oxidation since the oxidation potentials of substrates (**1a** and **2a**) and product **3a** are significantly higher than **8a** (Figure 1).

Scheme 4. Stoichiometric Reactions

Scheme 5. Mechanistic Study

Figure 1. Cyclic voltammograms recorded on a Pt electrode (area = 0.03 cm²). The scan rate was 100 mV s⁻¹: (a) MeCN containing 0.1 M *n*-Bu₄NPF₆; (b) MeCN containing 0.1 M *n*-Bu₄NPF₆, after addition of 4 mM **3a**; (c) MeCN containing 0.1

M *n*-Bu₄NPF₆, after addition of 4 mM **1a**; (d) MeCN containing 0.1 M *n*-Bu₄NPF₆, after addition of 4 mM complex **8a**; (e) MeCN containing 0.1 M *n*-Bu₄NPF₆, after addition of 4 mM (Cp^{*}IrCl₂)₂.

Based on our mechanistic studies, we propose a plausible catalytic cycle as shown in Scheme 6. Initially, C-H activation takes place to afford a cyclometallated Ir(III) intermediate **B**, following ligand exchange to deliver complex **C**. Next, migratory alkyne insertion results in the seven-membered iridium complex **D**,³² which undergoes reductive elimination to give Ir(I) complex **E**. Intermediate **E** is a coordinatively saturated, 18-electron complex. Upon anodic oxidation, product **3a** was realised from **E** and complex **A** is regenerated.

Scheme 6. Proposed Catalytic Cycle

In conclusion, we have demonstrated the first example of Ir-catalyzed electrochemical vinylic C-H annulation of acrylic acids with alkynes in an undivided cell. The method affords a variety of α -pyrones in good to excellent yields. Preliminary mechanistic experiments show that anodic oxidation is crucial for reoxidation of the diene-Ir(I) complex to an Ir(III) species with concomitant release of the product. Additional work on electrochemical vinylic C-H functionalization is currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Text, Figures, Tables, and CIF files giving experimental procedure, compound characterization data, and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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