

Electrooxidative Iridium-Catalyzed Regioselective Annulation of Benzoic Acids with Internal Alkynes

Qi-Liang Yang,[#] Hong-Wei Jia,[#] Ying Liu, Yi-Kang Xing, Rui-Cong Ma, Man-Man Wang, Gui-Rong Qu, Tian-Sheng Mei,* and Hai-Ming Guo*



socoumarins are not only important synthetic intermediates in complex heterocycle constructions, but also an integral and common part of many natural products and bioactive molecules.¹ Transition-metal-catalyzed oxidative annulations of benzoic acids with alkynes to construct the isocoumarin skeleton have been recognized as one of the most efficient synthetic approaches with the highest step- and atomeconomy.² Consequently, a series of classic transition metals including cobalt-,³ ruthenium-,⁴ rhodium-,⁵ and iridiumcatalyzed 5a,6 oxidative annulation have been well-developed. Despite indisputable advances, these coupling reactions usually require stoichiometric amounts of an external organic- or metal-based oxidant or an internal oxidizing group for catalyst turnover.⁷ The initial investigating chemical oxidants and the disposal of wastes at the end of the reaction remain challenges for these reactions, which compromise the synthetic utility and environmental merits of these approaches (Scheme 1a).

The merging of electrochemistry and transition-metal catalysis has been demonstrated as an attractive, powerful, and environmentally friendly strategy toward sustainable synthesis, featuring electricity as a waste-free and renewable oxidant or reductant.⁸ In this context, many elegant examples of electrochemically driven, metal-catalyzed sustainable C–H bond functionalization reactions have been developed.⁹ Nevertheless, to our knowledge, only a single example of electrochemical oxidative cyclization of internal alkynes with benzoic acids has been reported by the Ackermann group in 2018, employing ruthenaelectrocatalysis.¹⁰

Whereas electrochemical C–H activation catalyzed by $Rh(III)^{11}$ and $Ru(II)^{12}$ catalysts has been reasonably wellinvestigated, surprisingly little attention has been given to Cp*Ir(III) catalysts.¹³ Meanwhile, Cp*Ir(III) complexes have been identified as powerful catalysts that have enabled various

Scheme 1. Electrooxidative Ir-Catalyzed Regioselective Annulation

a. Schematic representation for transition-metal-catalyzed oxidative annulation



inert C-H functionalization reactions,¹⁴ featuring unique reactivities, great selectivities, and rich reaction types that

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could be well applied to late-stage modifications of bioactive molecules. Cp*Ir(III) catalysts should have great synthetic potential in C–H functionalization with electrochemistry. Given our continuous interest in site-selective C–H functionalization induced by metalla-electrocatalysis,¹⁵ we report herein an unprecedented iridium-catalyzed electro-oxidative annulation of easily accessible (hetero)aromatic acids with a wide array of internal alkynes through weak *ortho*-coordinating strategy (Scheme 1b).

We commenced our studies by using the 2-methylbenzoic acid 1a and diphenylacetylene 2a as the model substrates. By using 3 mol % $(Cp*IrCl_2)_2$ as the catalyst and 3.0 equiv of "Bu₄NOAc as the electrolyte, the annulation product 3a could be obtained in 90% isolated yield under 1.5 mA constant current in an undivided cell with two Pt plate electrodes at 60 °C. Methanol was identified as the optimal solvent. The combination of other solvents (EtOH, CF₃CH₂OH, and HFIP) with "Bu₄NOAc result in much lower yields (Table 1,

Table 1. Condition Optimization^a



^{*a*}Reaction conditions: two platinum plate electrodes (each 15 × 10 mm²), substrate **1a** (0.24 mmol, 1.2 equiv), alkyne **2a** (0.20 mmol, 1.0 equiv), "Bu₄NOAc (0.60 mmol, 3.0 equiv), (Cp*IrCl₂)₂ (3.0 mol %), MeOH (3.0 mL), 60 °C (oil bath temperature), 1.5 mA, and 12 h (3.4 F/mol). ^{*b*1}H NMR yields using CH₂Br₂ as an internal standard. ^cIsolated yields. ^{*d*}nr: no reaction.

entry 2). Keeping constant the electric quantity and raising the operating current to 3 or 6 mA would led to the reduced yields (Table 1, entry 3). Lowering the reaction temperature also resulted in deceased conversions (Table 1, entry 4). Carboxylate additives proved critical for the transformation. Switching "Bu₄NOAc to NaOAc or KOPiv provided similar results (Table 1, entry 5). In contrast, alternative electrolytes including "Bu4NBF4, "Bu4NPF6, and "Bu4NClO4 were entirely ineffective (Table 1, entry 6). Screening of electrods showed that both reticulated vitreous carbon and graphite felt could effectively substitute for platinum plate as the anode, but not graphite rod (Table 1, entry 7). This reaction could be readily scaled up to decagram scale, albeit in lower yield (Table 1, entry 8). Control experiments showed that both iridium catalyst (Table 1, entry 9) and electric current (Table 1, entry 10) were indispensable to the reaction.

With the optimized iridium-catalyzed electrooxidative C-H activation in hand, we sought to investigate the generality of

this methodology. Initially, we explored the reactivity of different alkynes 2 (Scheme 2). Highly coordinating dialkyl

Scheme 2. Ir-Catalyzed Electrochemical Annulation of Benzoic Acid 1a with Alkynes 2^{a-c}



^{*a*}Reaction conditions: substrate 1a (0.24 mmol, 1.2 equiv), alkyne 2 (0.2 mmol, 1.0 equiv), ^{*n*}Bu₄NOAc (0.60 mmol, 3.0 equiv), (Cp*IrCl₂)₂ (3.0 mol %), MeOH (3.0 mL), 60 °C (oil bath temperature), 1.5 mA, and 12 h (3.4 F/mol). ^{*b*}Isolated yields. ^{*c*}Regioselectivity ratio in parentheses. ^{*d*}5.0 mmol scale.

acetylenes such as hex-3-yne, oct-4-yne, and dec-5-yne gave products 3b-3d in excellent yields. When more sterically hindered arylalkynes were used instead of alkylalkynes, yields significantly decreased (3e-3k). Notably, asymmetrically substituted alkynes delivered the desired product in 6:1– 15:1 regioselectivities (3l-3x). Moreover, the protocol developed here could also find applications in the diversification of pharmacologically active molecules (3y), showcasing the potential utility of this chemistry.

The scope of benzoic acids was further examined under optimized conditions (Scheme 3). This robust iridium electrocatalysis displayed a remarkable tolerance to many sensitive, important, and valuable functional groups in the aromatic ring of benzoic acids, including alkyl, ether, fluoro, chloro, bromo, iodo, trifluoromethyl, nitro, hydroxyl, and ester substituents, setting the stage for subsequent late-stage diversifications. Generally, monosubstituted benzoic acids with electron-donating and electron-neutral substituents, such as methoxy, methyl, and halogen, readily reacted in satisfactory yields (4e-4o). Strong electron-withdrawing groups (CO₂Me, CF₃, and NO₂) afforded relatively lower yields due to lower conversion (4p-4r). As for substrates possessing a meta Scheme 3. Ir-Catalyzed Electrochemical Annulation of Benzoic Acid 1 with Alkynes $2c^{a,b}$



^aReaction conditions: substrate 1 (0.24 mmol, 1.2 equiv), alkyne 2c (0.2 mmol, 1.0 equiv), "Bu₄NOAc (0.60 mmol, 3.0 equiv), (Cp*IrCl₂)₂ (3.0 mol %), MeOH (3.0 mL), 60 °C (oil bath temperature), 1.5 mA, and 12 h (3.4 F/mol). ^bIsolated yields.

methyl group, annulation preferentially occurred at the less sterically congested C–H bond (4b). Moreover, heterocyclic carboxylic acids and indole-, furan-, and thiophenecarboxylic acids also efficiently participated in this transformation, leading to isocoumarins 4u-4w in 70, 73, and 33% yields, respectively.

To better define the generality of this methodology, we next extended the electrooxidative coupling reaction system to *tert*-propargyl alcohols **5**. To our delight, synthetically meaningful *tert*-propargyl alcohols **5** were smoothly converted into the corresponding isocoumarins **6** with excellent levels of regioselectivity under otherwise identical reaction conditions (Scheme 4). The tertiary hydroxyl group of propargylic alcohol plays a significant role for the observed reverse regioselectivity, probably due to its steric hindrance and binding affinity with the iridium catalyst.¹⁶

Gratifyingly, this electrooxidative coupling reaction could be further extended to the trifluoromethylated alkyne 7 shown in Scheme 5 using modified, basic conditions (see Table S6 in the Supporting Information). Using $(Cp*IrCl_2)_2$ as the catalyst (5 mol %) and CF_3CH_2OH as the solvent at 50 °C, the corresponding trifluoromethylated isocoumarins **8a–8c** were obtained in good yields with high levels of regioselectivity, generally placing the trifluoromethyl group in all cases proximal to the oxygen heteroatom. In sharp contrast, Rucatalyzed annulation under anodic oxidative conditions afforded **8b** in <5% yield (see the Supporting Information). It is important to note that this versatile iridium-catalyzed electrochemical alkyne annulation could serve as an alternative and complementary approach to the recently reported method.^{6,10}

The synthetic utility of this reaction was substantiated by an easily performed gram-scale reaction as demonstrated with the synthesis of 3c and 6l. The isocoumarin derivative 6a

Scheme 4. Ir-Catalyzed Electrochemical Annulation of Benzoic Acid 1 with *tert*-Propargyl Alcohols $5^{a,b}$



"Reaction conditions: substrate 1 (0.24 mmol, 1.2 equiv), alkyne 5 (0.20 mmol, 1.0 equiv), "Bu₄NOAc (0.60 mmol, 3.0 equiv), (Cp*IrCl₂)₂ (3.0 mol %), MeOH (3.0 mL), 60 °C (oil bath temperature), 1.5 mA, and 12 h (3.4 F/mol). ^bIsolated yields. ^c6.0 mmol scale.





"Reaction conditions: substrate 1 (0.20 mmol, 1.0 equiv), alkyne 7 (0.40 mmol, 2.0 equiv), "Bu₄NOAc (0.60 mmol, 3.0 equiv), $(Cp*IrCl_2)_2$ (5 mol %), CF_3CH_2OH (3.0 mL), 50 °C (oil bath temperature), 1.5 mA, and 10 h (2.8 F/mol). ^bIsolated yields. "Regioselectivity ratio in parentheses.

underwent smooth intramolecular cyclization when treated with BF₃:Et₂O to deliver indeno[2,1-c]isocoumarin **9** in 89% yield.^{6b} Furthermore, treatment of **9** with Lawesson's reagent,¹⁷ (NH₄)₂CO₃,¹⁸ and NaBH₄¹⁹ gave the corresponding thioisocoumarins **10**, 1(2*H*)-isoquinolone **11**, and chromene **12** in 85%, 80%, and 70% yields, respectively (see the Supporting Information, Scheme S1).

Several experiments have been performed to identify the reaction mechanism. To compare the activity of alkynes, the

treatment of benzoic acid 1a with diphenylacetylene 2a and oct-4-yne 2c was tested, affording 3a and 3c in a 1:2.5 ratio as determined from ¹H NMR analysis, indicating that the alkyl-substituted derivatives were converted preferentially (Scheme 6a). When an equimolar mixture of 1f and 1r was allowed to





c) KIE studies



d) Iridacycles 14 and 15 Synthesis



e) Catalytical reactivities of 14 and 15



f) Anodic oxidation of iridium(I) complex 15



competitively couple with 2c, products 4e and 4q were obtained in a 4:1 ratio, indicating that the electron-rich benzoic acid was more reactive than its electron-deficient counterpart. Next, an H/D exchange experiment was performed. Unlike previously reported anodic Ru catalysis,¹⁰ almost no loss of deuterium from $[D_5]$ -1b was observed, which indicates the good stability of the C–Ir bond (Scheme 6b). A large kinetic isotope effect ($k_{\rm H}/k_{\rm D} = 3.0$) was obtained in an intermolecular

competition experiment. In addition, a KIE value of ~ 1.6 was observed from a parallel single-component experiment using 1b and $[D_5]$ -1b (Scheme 6c). These results suggested that the cleavage of C-H was probably involved in the rate-limiting step. Subsequently, stoichiometric reactions were carried out. The metalacycle intermediate 14 was isolated with good yield in the reaction of 1a with $IrCp^*(OAc)_2(DMSO)$ ²⁰ Then the cyclometalated complex 14 was treated with 2a in the absence of electricity, which gave the sandwich complex 15 with isocoumarin 3a as the neutral ligand. This observation is a strong testament to the facile reductive elimination of the seven-membered iridacycle intermediate (Scheme 6d). Notably, both complexes 14 and 15 proved to be catalytically competent species in the electrooxidative annulation. (Scheme 6e). Thereafter, the key reoxidation of the iridium(I) sandwich complex 15 was probed by anodic oxidation in stoichiometric experiments. When Ir(I) complex 15 was subjected to electrolysis, 3a was obtained in 96% yield (Scheme 6f). This result provided compelling evidence for the efficient anodic oxidation of the iridium(I) intermediate by electrochemical approach.

Finally, we carried out cyclic voltammetry studies (Figure 1). The oxidation potentials of 2-methylbenzoic acid 1a,



Figure 1. Cyclic voltammograms recorded in MeCN with 0.1 M ${}^{n}\text{Bu}_4\text{NPF}_6$ as the supporting electrolyte: scan rate, 100 mV s⁻¹, substrate (4 mM), Pt electrode (area = 0.03 cm²) as the working electrode, SCE as the reference electrode.

diphenylacetylene 2a, and isocoumarin 3a were found at 2.69, 1.88, and 1.74 V versus SCE, respectively, while iridacycle 15 showed a significantly lower oxidation potential at 0.79 V versus SCE (curve e, Figure 1), indicating an initial anodic iridium(I/III) oxidation with a concomitant release of 3a. In light of preliminary experimental investigations and precedent literatures,^{6,16} a possible catalytic cycle is proposed (see Supporting Information, Scheme S3).

In conclusion, we have developed an electricity-powered, Cp*Ir(III) catalyst enabled regioselective annulative coupling of benzoic acids with internal alkynes. This technology circumvents the need for external chemical oxidants and ensures broad reaction compatibility with a wide range of sterically and electronically diverse substrates, allowing facile access to diversely functionalized isocoumarins in a highly regioselective manner. Preliminary mechanistic studies provide support for the facile organometallic C–H bond activation and the effective anodic oxidation of the iridium(I) intermediate. Further investigations aimed at developing more electrooxidative Ir-catalyzed C–H activations are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04168.

General information, experimental details, X-ray data, and NMR spectral data (PDF)

Accession Codes

CCDC 1878736, 1920134, 2014257, 2014259, 2014285, 2036876, 2043553, and 2052477 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

- Tian-Sheng Mei State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China; orcid.org/0000-0002-4985-1071; Email: mei7900@sioc.ac.cn
- Hai-Ming Guo Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China; orcid.org/ 0000-0003-0629-4524; Email: ghm@htu.edu.cn

Authors

- Qi-Liang Yang Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China; orcid.org/ 0000-0003-4734-5391
- Hong-Wei Jia Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China
- Ying Liu Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China
- Yi-Kang Xing State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

- Rui-Cong Ma Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China
- Man-Man Wang Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China
- Gui-Rong Qu Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c04168

Author Contributions

[#]Q.-L.Y. and H.-W.J. contributed equally.

Notes

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The authors declare no competing financial interest.

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