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Electrooxidative iridium-catalyzed sp^2 C–H activation–annulation leading to cationic π-extended heteroaromatics†

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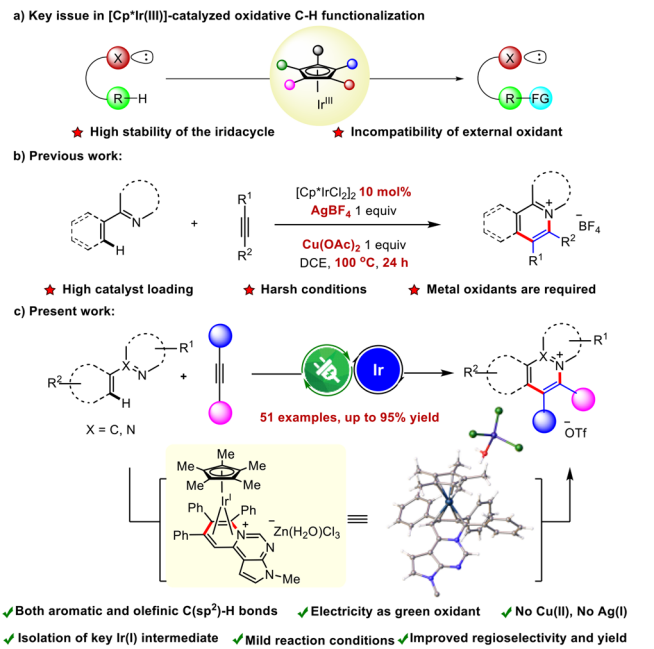
This study demonstrates an electrochemically driven, Ir(III)-catalyzed method for pyridine-, azo-, and purine-directed olefinic and aromatic C(sp^2)–H activation and regioselective annulation with alkynes for the synthesis of biologically useful quaternary ammonium salts. This approach notably eliminates the need for stoichiometric amounts of external oxidants, offering a broader substrate scope along with improved product regioselectivity under mild electrolysis conditions as compared to previously employed strong oxidant conditions. Detailed mechanistic insights, including the isolation, characterization, and cyclovoltammetric analysis of catalytically relevant iridium(III) and iridium(I) intermediates, provided strong supporting evidence for an Ir(III/I) catalytic cycle operation.

Introduction

Cyclometalated iridium(III) half-sandwich complexes have consistently received attention from the chemical community owing to their versatile catalytic efficiency and great synthetic potential for various chemical transformations.[1] However, in the realm of oxidative C–H functionalizations, Cp*Ir(III) metallacycles have been observed to be catalytically inactive, despite these isolable Ir(III) complexes being recognized for their participation in C–H activation processes in a stoichiometric fashion.[2] This inactivity is primarily attributed to two key issues:[3] (i) the high stability of the iridacycle intermediates and (ii) the incompatibility of external oxidants with iridacycles (Scheme 1a). In recent years, metallaelectrocatalysis,[4] which combines electrosynthesis and transition metal catalysis, has emerged as a powerful and enabling tool in organometallic C–H activation.[5] This approach employs cost-effective and renewable electricity to modify the oxidation state of metal catalysts.[6] The emergence of metallaelectrocatalysis has provided new opportunities for Cp*Ir(III)-catalyzed C–H activation reactions. The Ackermann group reported the first instance of dual iridium and electrocatalysis for C–H alkenylation *via* weak O-assistance in 2018.[7] Later, Mei *et al.* presented the first example of Ir-catalyzed electrooxidative vinylic C–H annulation of acrylic acids with alkynes.[8] Chang *et al.* also



Scheme 1 Synthesis of cationic polycyclic heteroaromatic compounds *via* iridium-catalyzed electrooxidative C–H activation/annulation.

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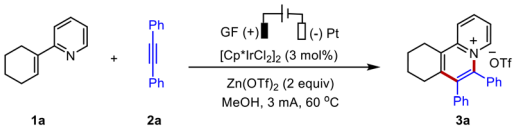
documented an electrochemical intramolecular dehydrogenative C–H/N–H coupling, using a Cp*Ir catalyst, to synthesize N–H indoles.[9] However, electrochemical C–H activations using Cp*Ir(III)[10] catalysts remained underexplored as compared to their congener Cp*Rh(III)[11] catalysts.

Cationic π-conjugated organic molecules are frequently found in the core structures of numerous pharmaceuticals, bioactive compounds, and organic materials.[12] A straightforward and efficient synthetic route to this class of compounds includes the annulative alkyne-insertion π-extension (AAIPEX) strategy, which employs simple (hetero)arene templates and alkynes as π-extending partners.[13] Compared to other versatile transition-metal catalysts such as rhodium,[14] ruthenium,[15] and cobalt,[16] which have well demonstrated their efficiency in AAIPEX reactions for various cationic polycyclic heteroaromatic compounds (cPHACs), the potential of the Cp*Ir(III) catalyst in this domain is still under development. In 2016, the Wang group[17] successfully demonstrated a Cp*Ir(III) catalyzed oxidative annulation of N-heterocycles/imines with alkynes, employing $AgBF_4$ and $Cu(OAc)_2$ as stoichiometric co-oxidants at 100 °C (Scheme 1b). However, the high catalyst loadings, elevated temperature, prolonged reaction time, and stoichiometric amounts of metal oxidants essential for this procedure compromised its synthetic utility. As a result, developing efficient and mild AAIPEX procedures that allow the utilization of Cp*Ir(III) remains an important research goal.

As part of our continuing interest in developing sustainable C–H functionalization,[18] we recently conducted the Cp*Ir(III)-catalyzed regioselective annulation of various olefinic, aromatic, and heteroaromatic substrates with alkynes for the synthesis of cPHACs under mild electro-oxidative conditions (Scheme 1c). The salient features of this work comprise (a) a versatile iridaelectro-catalytic system, (b) high regioselectivities, (c) a broad substrate scope with alkenes, arenes, and internal alkynes, even in the context of late-stage functionalization, (d) isolation and full characterization of key sandwich iridium(I) intermediates, and (e) detailed mechanistic insights into iridaelectro-catalysis.

Initially, the effects of different electrochemical conditions on the Cp*Ir(III)-catalyzed coupling of 2-(cyclohex-1-en-1-yl) pyridine (**1a**) with 1,2-diphenylethyne (**2a**) were studied. Pleasingly, the target product **3a** was obtained with a 92% ^{1}H NMR yield in the presence of 3 mol% of $[Cp^*IrCl_2]_2$ as the catalyst. An undivided cell with a graphite felt anode and a platinum cathode with a constant current of 3 mA was used for the reaction and the product was obtained after 8 h in MeOH at 60 °C (Table 1, entry 1, please refer to the ESI† for more details). Using HOTf, NaOTf, or KOTf to replace $Zn(OTf)_2$ led to reduced yields (entry 2). When mixed solvents such as $CF_3CH_2OH : H_2O$ and $HFIP : H_2O$ were used, the yield significantly declined (entries 3 and 4). Using EtOH also resulted in a diminished yield of **3a** (entry 5). Also, when the reaction was conducted at 1 mA and 5 mA, the yield slightly decreased (entry 6). When the graphite felt of the anode was replaced by a Pt plate or graphite rod, the yields dropped to 87% and 42%, respectively (entry 7). Notably, a similar result was obtained

Table 1 Selected optimization studies[a]



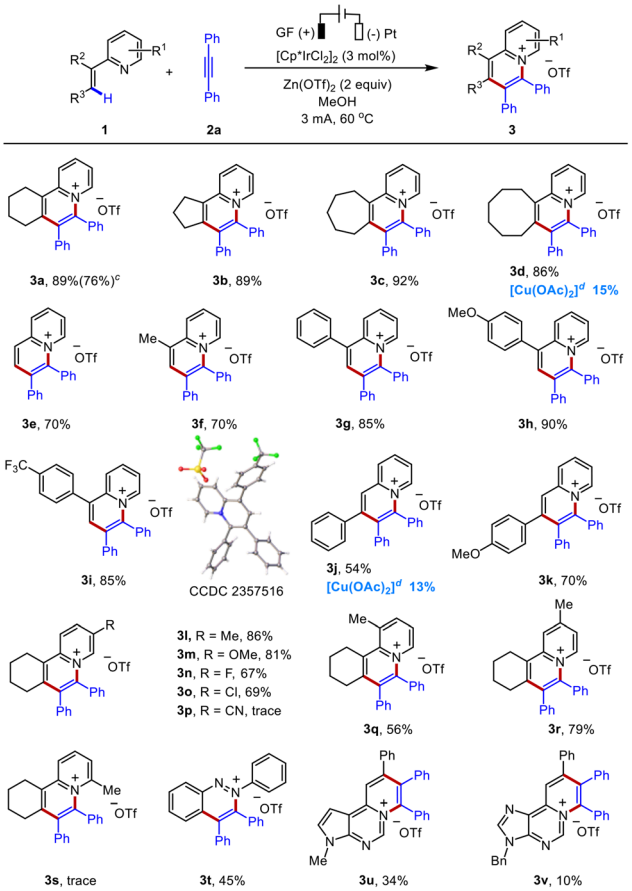
1a 2a 3a

Entry	Deviation from standard conditions	Yield[b] [%]
1	None	92(89)[c]
2	HOTf, NaOTf, or KOTf instead of $Zn(OTf)_2$	67, 21, 13
3	$CF_3CH_2OH : H_2O$ instead of MeOH	38
4	$HFIP : H_2O$ instead of MeOH	36
5	EtOH instead of MeOH	78
6	1 mA, 25 h or 5 mA, 5 h	78, 89
7	Pt, graphite rod, or RVC as anode	87, 42, 92
8	Reaction at 27 °C or 45 °C	57, 76
9	$[Cp^*IrCl_2]_2$ (2 mol%)	48
10	Without [Ir]	nr[d]
11	Without electric current	nr[d]
12	$Cu(OAc)_2$ or AgOAc instead of electric current	4, 7

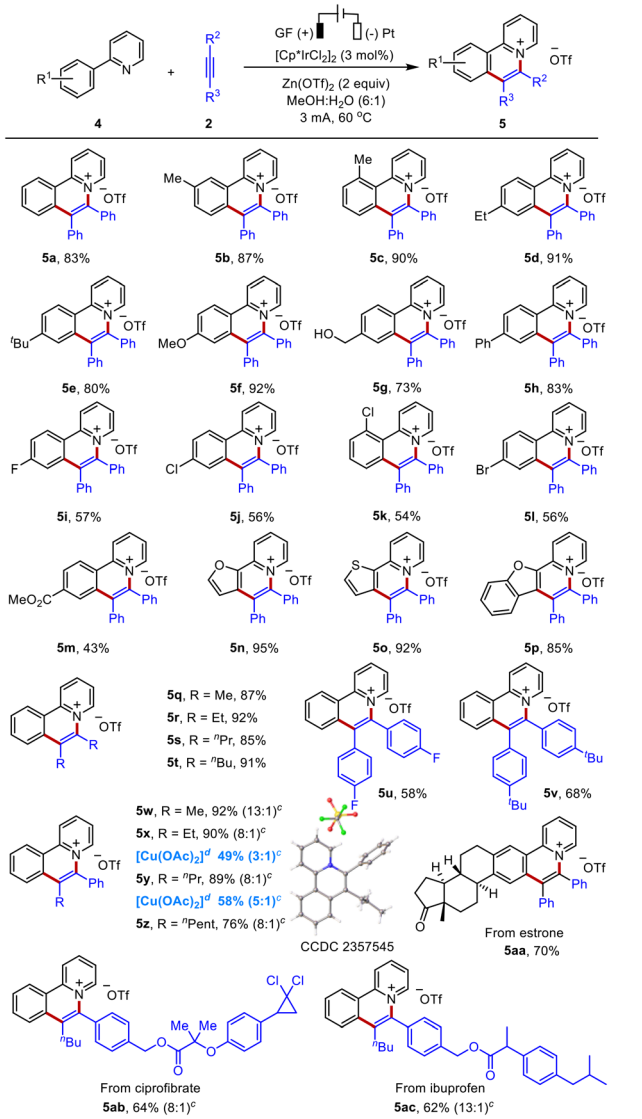
[a] Standard conditions: $[Cp^*IrCl_2]_2$ (3 mol%), **1a** (0.2 mmol), **2a** (0.3 mmol), MeOH (3 mL), $Zn(OTf)_2$ (2 equiv., 0.4 mmol), 60 °C, 3 mA, 8 h. [b] Yields determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Yields of isolated products. [d] nr: no reaction.

when reticulated vitreous carbon (RVC) was used as the anode. When the reaction was carried out at a decreased temperature (27 °C or 45 °C), the desired product **3a** was obtained in inferior yields of 57% and 76%, respectively (entry 8). Decreasing the catalyst loading from 3 mol% to 2 mol% significantly slowed the reaction, yielding a mere 48% of **3a** (entry 9). In the absence of the iridium catalyst and electric current, the reaction failed to proceed (entries 10 and 11). Notably, the replacement of electric current with the heavy metal oxidant $Cu(OAc)_2$ or AgOAc under the standard conditions failed to give acceptable yields, reflecting the unique efficacy of the electrocatalysis (entry 12).

With the optimized electrolytic conditions, the scope of 2-alkenylpyridines was investigated. First, 2-pyridyl-substituted five- to eight-membered cycloalkenes were tested. Their reactions with 1,2-diphenylethyne (**2a**) resulted in the desired products (**3a–3d**) in 86–92% isolated yields (Scheme 2). 2-Vinylpyridines **1e** and **1f**, having methyl substitution at the α-carbon, also reacted smoothly with **2a**, providing **3e** and **3f** in 70% yields, respectively. The reaction tolerated the vinylpyridines having α-aryl substitutions regardless of their electronic properties, yielding the corresponding products **3g–3i** in 85 to 90% yields. The β-substituted vinylpyridines **1j** and **1k** also yielded the expected quinolizinium salts **3j** and **3k** in 54% and 70% yields, respectively. Next, the effect of the substituents of the pyridyl ring on this transformation was also examined. It was found that the substrates bearing electron-donating groups (5-Me, 5-MeO) and mild electron-withdrawing groups (5-F, 5-Cl) on the pyridyl ring gave the corresponding products (**3l–3o**) in moderate to good yields (67–86%). Contrastingly, a strong electron-withdrawing group (5-CN) completely inhibited the reaction (**3p**). Apart from the electronic effects, this trans-



Scheme 2 Substrate scope of the electrochemical Ir(III)-catalyzed annulation of a nonaromatic sp^2 C–H bond. Standard conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*IrCl_2]_2$ (3 mol%), $Zn(OTf)_2$ (2 equiv., 0.4 mmol), MeOH (3 mL), undivided cell, 60 °C, 3 mA. Yields of isolated products. [a] Gram scale (see the ESI† for details). [b] Yields are from reactions under Wang's conditions (ref. 17).



Scheme 3 Substrate scope of the electrochemical Ir(III)-catalyzed annulation of an aromatic sp^2 C–H bond. Standard conditions: **4** (0.2 mmol), **2** (0.3 mmol), $[Cp^*IrCl_2]_2$ (3 mol%), $Zn(OTf)_2$ (2 equiv., 0.4 mmol), 3.5 mL of solvent ($MeOH/H_2O$ = 6/1), undivided cell, 60 °C, 3 mA. Yields of isolated products. [a] Ratios of regioisomers (given in parentheses) were determined by ^1H NMR analysis. [b] Yields are from reactions under Wang's conditions (ref. 17).

formation was also apparently sensitive to the steric hindrance of the substituents on the pyridine moiety. Compared to methyl substitution at the 3, 4, or 5-position of the pyridyl ring, which resulted in good yields (**3q**, 56%, **3r**, 79%, and **3l**, 86%), the substitution at the 6-position completely inhibited the reaction (**3s**, trace). In addition, azobenzene, 7-deazapurine, and purine can also act as auxiliary groups, but they are less effective than pyridine, yielding **3t** (45%), **3u** (34%) and **3v** (10%).

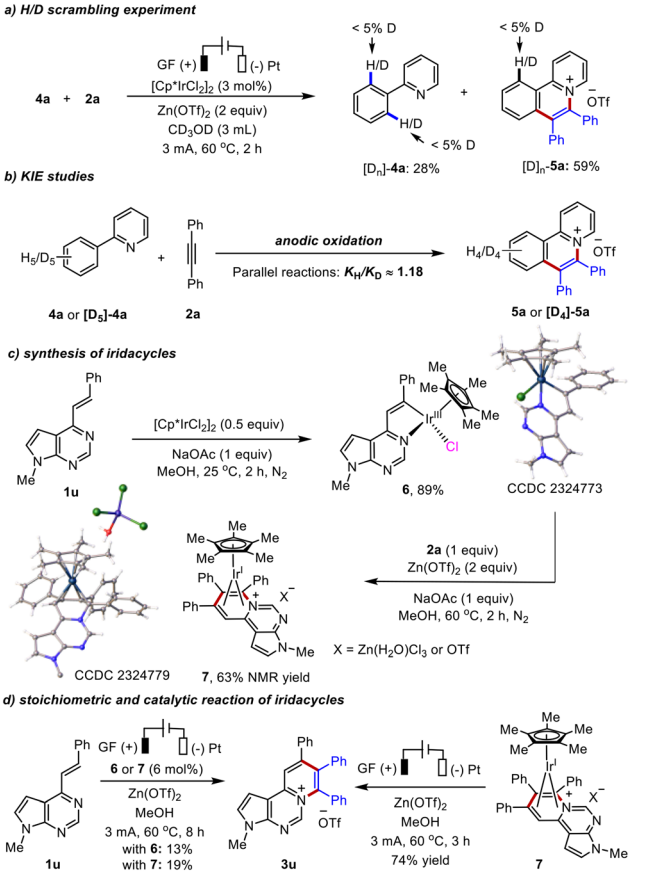
To our delight, it was then found that this strategy could be extended to (hetero)arene substrates under slightly modified conditions using a mixed solvent of $MeOH/H_2O$ (6 : 1) (Scheme 3). The reaction tolerated a wide range of arene substrates regardless of their electronic properties and substitution patterns, and the corresponding products **5a–5m** were obtained in 43% to 92% yields. The substrate bearing an *m*-methyl substituted phenyl group (**4b**) underwent selective *ortho* C–H activation at the less hindered C–H bond, furnishing product **5b** in 87% yield. The sterically hindered *ortho*-substituted substrate **4c** also yielded the expected product **5c** in 90% yield. 2-Phenylpyridines with an ethyl, *tert*-butyl, methoxy, hydroxymethyl, or phenyl group at the *para*-position of the benzene ring gave the corresponding products in good to excellent yields (**5d–5h**), whereas those bearing a fluoro, chloro, bromo, or ester group at the *para*- or *ortho*-position exhibited comparatively modest results (**5i–5m**). In addition, 2-furyl-, 2-thienyl-, and 2-benzofuryl-substituted pyridines also showed good reactivity and gave the desired products **5n**, **5o**, and **5p** in excellent yields of 95%, 92%, and 85%, respectively. The aliphatic alkyne substrates yielded the desired products in good to excellent yields, as indicated by the conversions of but-2-yne, hex-3-yne, oct-4-yne, and dec-5-yne to provide the

corresponding **5q–5t** in 85–92% yields. Internal diarylalkynes containing fluoro and *tert*-butyl substituents at the *para*-position of the phenyl ring gave **5u** and **5v** in 58% and 68% yields, respectively. Moreover, unsymmetrical aryl alkyl-disubstituted alkynes demonstrated high reactivity and good regioselectivity (**5w–5z**), placing the aliphatic substituents distal to the nitrogen. Substrates derived from complex molecules were also tested for the generality of this method. For example, a pyridine-containing estrone derivative or alkyne-bearing ciprofibrate and ibuprofen motifs were also tested for this reaction. The corresponding products **5aa–5ac** were obtained in satisfactory yields (62–70%) with high to excellent regioselectivity.

To assess the efficacy of the disclosed method relative to Ir-catalyzed annulation using chemical oxidants at elevated temperatures, the obtained results were directly compared with the results of the original Wang procedure.[17] While the annulation of 1,2-diphenylethyne (**2a**) with 2-(cyclooct-1-en-1-yl)pyridine (**1d**) and 2-styrylpyridine (**1j**) was found to be inefficient under a chemical approach, furnishing **3d** and **3j** in poor yields (15% and 13%), it was found to be highly efficient under an electrochemical approach, affording **3d** and **3j** in 86% and 54% yields, respectively, within 8 hours at 60 °C. In addition to exhibiting a more expansive substrate scope, our method substantially improved regioselectivity with unsymmetrical internal alkynes. As such, Ir-catalyzed annulation with chemical oxidants yielded the products **5x** and **5y** with regioselectivities of 3 : 1 and 5 : 1, respectively, while the electrochemical cyclization resulted in an 8 : 1 regioselectivity for both products. These results clearly demonstrated the advantages of this electrochemical method.

To investigate the mechanism, H/D exchange experiments were performed in the presence of CD_3OD as the solvent. No obvious deuterium incorporation was found in either the unreacted **4a** or the product **5a**, suggesting that the iridium-catalyzed C–H activation step was largely irreversible (Scheme 4a). A primary kinetic isotope effect (KIE) of about 1.18 was observed for the parallel experiment, indicating that C–H bond cleavage may not be the rate-determining step (Scheme 4b). These observations are in sharp contrast to those of the rhoda-[11g,j] and ruthena-electrocatalysis.[18a] Upon treatment of substrate **1u** with $[Cp^*IrCl_2]_2$ in the presence of NaOAc at room temperature, a five-membered cyclometalated iridium complex **6** was formed in 89% yield (Scheme 4c). Furthermore, the stoichiometric reaction of iridacycle **6** with the alkyne **2a** and $Zn(OTf)_2$ at 60 °C directly produced the low valent iridium (I) sandwich complex **7** with $Zn(H_2O)Cl_3$ or OTf as a counter ion, the identity of which was confirmed using ^1H and ^{13}C NMR spectra as well as X-ray diffraction analysis. Notably, it was found that these two well-defined iridium complexes were competent catalysts for this reaction (Scheme 4d, left). The complex **7** under electrolysis smoothly generated **3u** in 74% yield (Scheme 4d, right). These discoveries indicated that both iridacycles **6** and **7** are crucial intermediates in the catalytic cycle.

As observed from the cyclic voltammetry experiments (Fig. 1), the oxidation peaks of the substrates **1u** and **2a**, as



Scheme 4 Mechanistic studies.

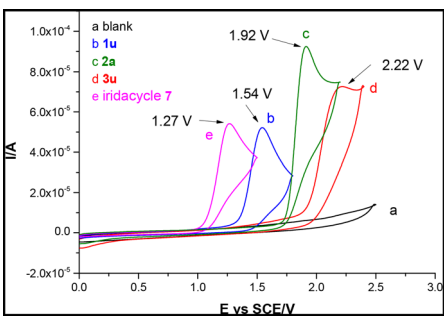
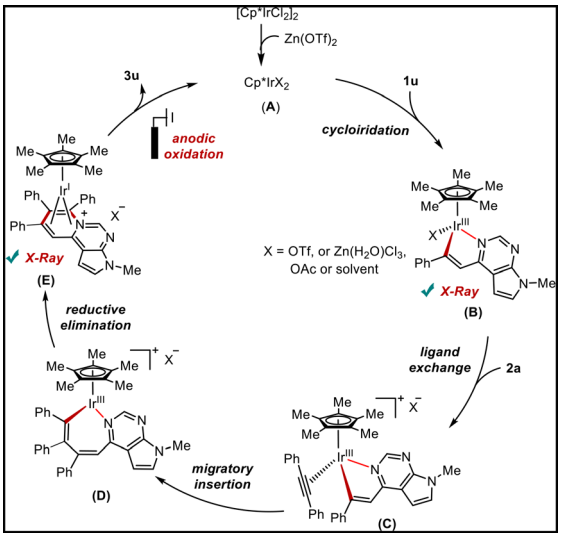


Fig. 1 Cyclic voltammetry studies. Conditions: **1u** (2 mM), **2a** (2 mM), **3u** (2 mM), and iridacycle **7** (2 mM), $^nBu_4NPF_6$ (0.1 M), MeCN, 0.1 V s^{-1}.

well as the product **3u**, were found at approximately 1.54, 1.92, and 2.22 V *vs.* SCE, respectively, in MeCN, while iridacycle **7** showed a lower oxidation potential at around 1.27 V *vs.* SCE. These results suggest that once iridacycle **7** is formed, it is preferentially oxidized at the anode.

Based on the abovementioned results, a proposed mechanism for the Cp*Ir(III)-catalyzed oxidative annulation reaction is depicted in Scheme 5. Initially, the dimeric catalyst $[Cp^*IrCl_2]_2$ is converted to an active cationic catalyst $[Cp^*Ir(III)]^{2+}$ (**A**) by $Zn(OTf)_2$, facilitating the cyclo-iridation of **1u** to afford a five-membered iridacycle intermediate **B**. Then,



Scheme 5 Plausible reaction mechanism.

π coordination of the alkyne to form **C** and subsequent regioselective migratory insertion give a seven-membered ring iridacycle **D**. Upon rapid reductive elimination, the key intermediate iridium(I) sandwich complex **E** is formed. Finally, the reduced iridium(I) species is re-oxidized to iridium(III) at the anode, releasing the quaternary ammonium salt **3u** and generating H_2 as the by-product at the cathode. During the catalytic process, an equivalent amount of the OTf anion is essential for isolating the final salt.

Conclusions

In summary, an electrooxidative Ir(III)-catalyzed method for activating and functionalizing the typically inert C(sp^2)–H bonds in olefinic and aromatic compounds using various internal alkynes has been successfully developed. The reaction produced various important cationic π-extended heteroaromatics in moderate to good yields. This protocol circumvents the limitations of previous iridium catalytic systems and features mild conditions, a broad substrate scope of both arenes and alkenes, environmentally benign electrolysis, a high level of regioselectivity, and compatibility with biologically active compounds. The reaction mechanism was fully studied through H/D exchange experiments, KIE, and isolation of novel iridium(I) sandwich intermediates. These findings should prove instrumental for the mechanistic understanding and reaction design of iridium(III)-catalyzed electro-oxidative C–H functionalizations.

Data availability

The authors declare that the data supporting the findings of this study are available within the paper and its ESI,† and are also available from the corresponding author. The nuclear magnetic resonance (NMR), experimental procedures and characterization for all products, mechanism studies are shown in the ESI.† The X-ray crystallographic coordinates for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 2324773 (for **6**), CCDC 2324779 (for **7**), CCDC 2357516 (for **3i**), and CCDC 2357545 (for **5y**).†

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

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