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Electrosynthesis

Distal Ruthenaelectro-Catalyzed *meta*-C–H Bromination with Aqueous HBr

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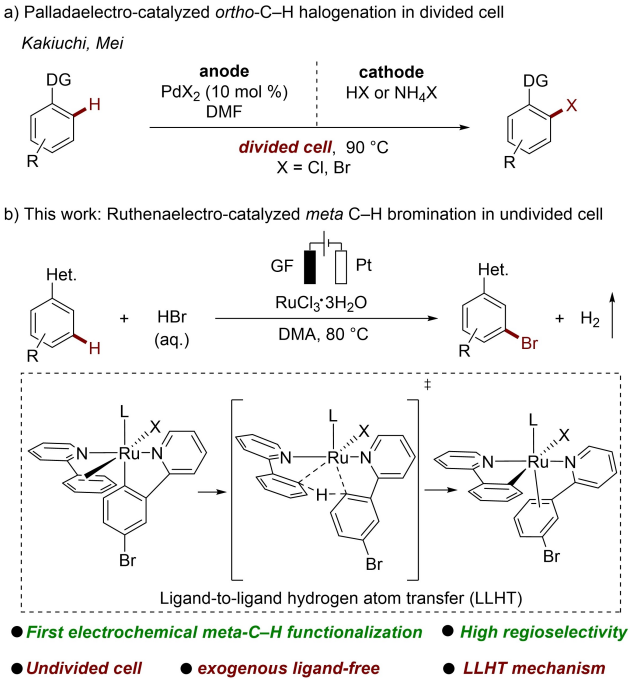
Abstract: While electrochemical *ortho*-selective C–H activations are well established, distal C–H activations continue to be underdeveloped. In contrast, we herein describe the electrochemical *meta*-C–H functionalization. The remote C–H bromination was accomplished in an undivided cell by $RuCl_3{\cdot}3H_2O$ with aqueous HBr. The electrohalogenation proceeded under exogenous ligand- and electrolyte-free conditions. Notably, pyrazolylarenes were *meta*-selectively brominated at the benzenoid moiety, rather than on the electron-rich pyrazole ring for the first time. Mechanistic studies were suggestive of an initial ruthenacycle formation, and a subsequent ligand-to-ligand hydrogen transfer (LLHT) process to liberate the brominated product.

Introduction

Electro-organic synthesis has emerged as an increasingly powerful tool for molecular syntheses with electricity as an atom-economic redox reagent, avoiding the use of traditional chemical redox agents.[1,2] Particularly, the merger of electrocatalysis with organometallic chemistry has set the stage for arene *ortho*-C–H functionalizations,[3] with key contributions by the groups of Mei,[4] Kakiuchi,[5] Xu,[6] Lei[7] and Ackermann,[8] among others (Scheme 1a).[9] In contrast, while methods for distal C–H functionalization are in high demand,[10–14] the remote arene diversification by metallaelectro-catalyzed C–H functionalization has thus far proven to be elusive. In addition, to avoid reduction of transition-metal cation at the cathode, bidentate directing groups and/or divided cell setups were predominately exploited.



Scheme 1. Transition-metal-catalyzed aryl C–H bromination.

Aryl halides serve as versatile functionalities to a rich array of value-added chemicals and materials, including pharmaceutical intermediates and polymers.[15] Transition metal-catalyzed regioselective C–H halogenations were developed to prepare aryl halides generally using corrosive reagents combined with stoichiometric external strong chemical oxidants.[16] With electricity as the oxidant, Kakiuchi[5] and Mei[4b,c] reported palladaelectro-catalyzed *ortho*-C–H halogenation with divided cell setups being required (Scheme 1a). In sharp contrast, we herein report on a uniquely efficient electrochemical ruthenium-catalyzed *meta*-C–H bromination (Scheme 1b). Salient features of our strategy comprise a) the first metallaelectro-catalyzed *meta*-C–H functionalization, b) $RuCl_3{\cdot}3H_2O$ as the catalyst, c) user-friendly aqueous HBr as the brominating source, d) an undivided cell set-up, e) high regioselectivities for challenging pyrazolylarenes, and f) mechanistic studies supporting a new LLHT regime.

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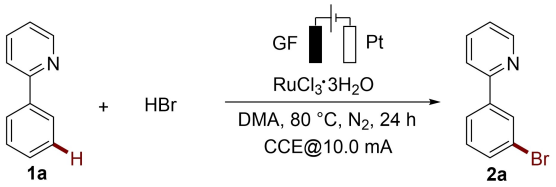
Results and Discussion

We initiated our studies by exploring the envisioned bromination of arene **1a** using graphite felt (GF) and platinum plate (Pt) as anode and cathode material, respectively (Table 1). After considerable experimentation, the desired bromination product **2a** was obtained in 83% isolated yield with $RuCl_3{\cdot}3H_2O$ as the catalyst and aqueous HBr as brominating agent in an undivided cell set-up (Entry 1). Various solvents were tested, showing that *N*,*N*-dimethylacetamide (DMA) was performing best (Entry 2). The bromination reaction was not viable with TBABr or LiBr, but occurred with HBr/HOAc, indicating that the acidic conditions played a key role for the electrocatalysis (Entries 3 and 4). Substrate **1a** was fully converted into *meta*-bromo product **2a** in 20 h when increasing the current from 10 mA to 12 mA (Entry 6). Notably, *ortho*-bromination and dibromination byproducts were not observed (see Figure S1). Control experiments showed that both the electricity and the ruthenium catalyst were essential for the electrochemical bromination (Entry 8). $RuBr_3$ was also effective for the desired *meta*-C–H bromination (Entry 9). Reactions with other transition metal catalysts, including $OsCl_3$, $RhCl_3$ and $MnBr_2$, have also been probed, but none of these salts was effective for the C–H bromination (Entry 10). In addition, aqueous HCl and HI were not suitable for the halogenation reaction (See Figure S3).

With the optimized reaction conditions in hand, the viable substrate scope of the ruthenaelectro-catalyzed *meta*-C–H bromination was explored next (Scheme 2). A range of pyridylarenes **1a**–**1n** bearing various substituents could be selectively brominated using aqueous HBr as the bromination source. Functional groups, including ether, thioether, silyl and fluoro, chloro and bromo were tolerated (**2b**–**2n**). Generally, electron-rich substrates reacted more efficiently than the electron-deficient analog. Other heteroarenes, including phenylpyrimidine **1o**, benzo[*h*]quinoline **1p** and purine derivatives **1q**–**1r**, were identified as amenable substrates for the electrochemical remote C–H bromination.

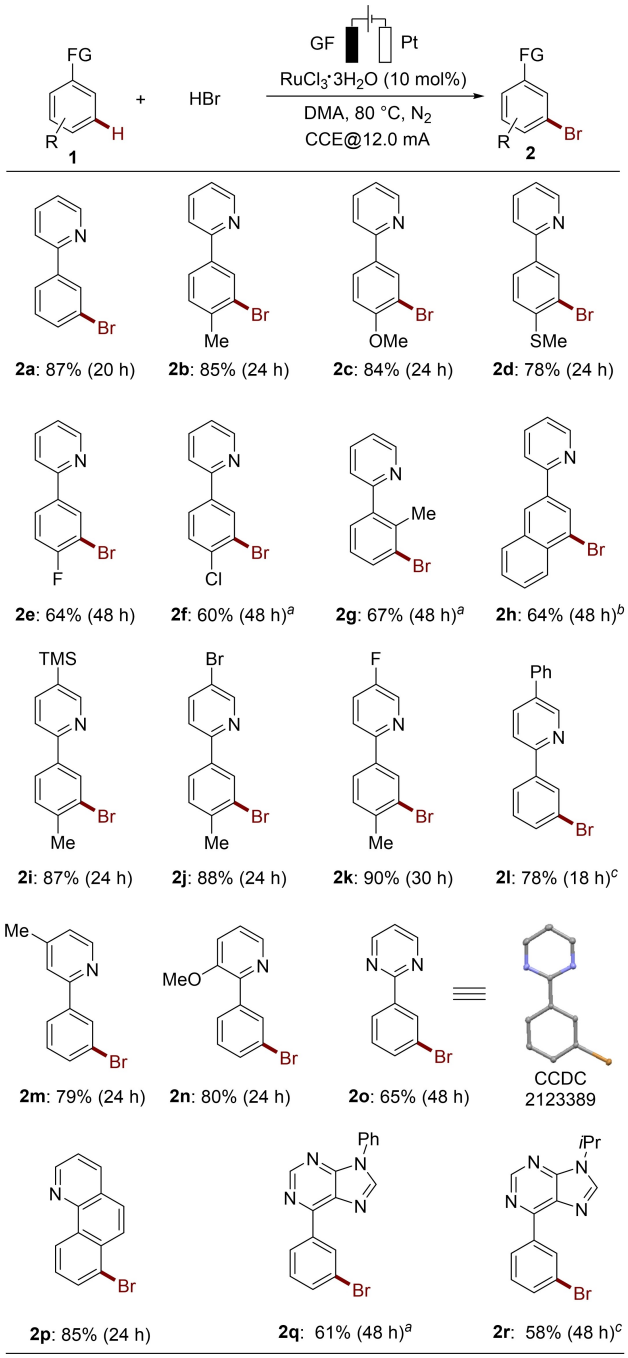
The selective bromination of pyrazolylarenes is challenging. Reported strategies under ruthenacatalysis[14c,17] or electrochemical metal-free[18] conditions were shown to selectively occur on the electron-rich pyrazole heterocycle.

Table 1: Optimization of the ruthenaelectro-catalyzed *meta*-C–H bromination.[a]



Entry	Variation from standard conditions	**2a** [%][b]
1	no change	83
2	CH_3CN or DMSO as solvent	0
3[c]	LiBr or TBABr in place of HBr	trace
4	HBr in HOAc in place of aq. HBr	81
5	CCE@5.0 mA	58
6	CCE@12.0 mA, 20 h	87
7	2.5 equiv HBr, 12 mA	86
8	no electricity, no [Ru]	trace, 0
9	$RuBr_3$ as catalyst, 12 mA	87
10	$MnBr_2$, $OsCl_3$ or $RhCl_3$ as catalyst	0

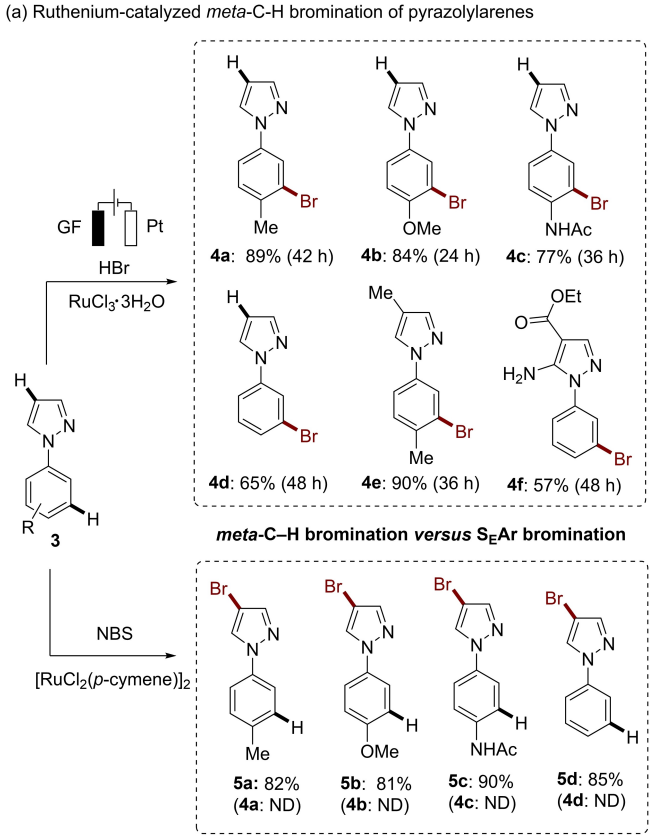
[a] Undivided cell, GF anode, Pt cathode, constant current = 10.0 mA, **1a** (0.50 mmol), HBr (48% aqueous solution, 2.0 mmol, 220 µL), $RuCl_3{\cdot}3H_2O$ (0.05 mmol), solvent (5.0 mL), N_2, 24 h, work-up with Et_3N (2 mL) and pyridine (1.5 mL). [b] Yields of isolated product **2a**. [c] H_2O (100 µL) as additive.



Scheme 2. Ruthenaelectro-catalyzed *meta*-C–H bromination. [a] 90 °C. [b] $RuBr_3$ as catalyst. [c] HBr (2.5 equiv), under air, 10 mA.

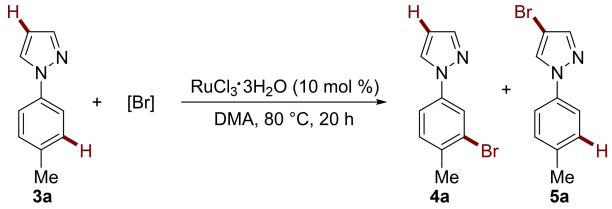
In sharp contrast, by the ruthenaelectro-catalysis the pyrazolylarenes **3a**–**3f** were for the first time selectively brominated at the benzenoid moiety, rather than on the pyrazole motif (Scheme 3a). In sharp contrast, when the previously reported NBS/[$RuCl_2$(*p*-cymene)] catalysis was applied for substrates **3a**–**3d**, the bromination only occurred on the pyrazole rings via a simple S_EAr, and the desired *meta*-C–H bromination was not observed (Scheme 3a). In addition, the $RuCl_3$-catalyzed bromination of pyrazolylarene **3a** with different brominating agents, such as NBS, $TBABr_3$ and Br_2, were further tested but failed to give the desired *meta*-product (Scheme 3b and Figure S2).

The practical utility of this ruthenaelectro-catalyzed *meta*-C–H bromination was illustrated by a gram-scale preparation (Scheme 4a) as well as the subsequent diversification of the newly installed bromo group in various C–C couplings. Thereby, we successfully achieved the selective indirect C–H alkenylation and arylation (Scheme 4b). Furthermore, sequential twofold C–H functionalization involving *meta*-bromination and *ortho*-arylation was achieved in a one-pot fashion (Scheme 4c). In addition, while the pyridine ring could be efficiently converted into piperidine and 2-formylpyrrole (Scheme 4d), the pyrazolylmotif was removed to deliver synthetically meaningful anilines (Scheme 4e).



ND = not detected. For experimental details see the Supporting Information

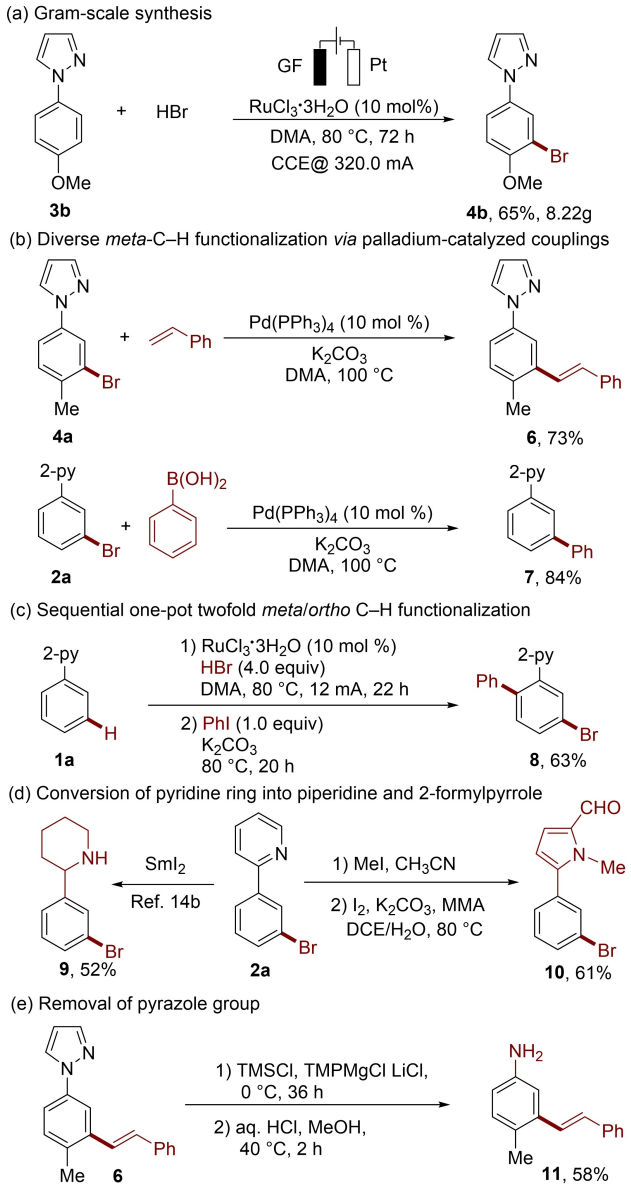
(b) Bromination of pyrazolylarene **3a** under different conditions*



Entry	Brominating agent	Conv. (%)	**4a**/**5a**
1	NBS (1.5 equiv)	> 95%	**<1/99**[a]
2	Br_2 (1.5 equiv)	> 95%	12/88[a]
3	HBr (4.0 equiv)/Br_2 (1.5 equiv)	> 95%	16/84[a]
4	HBr (4.0 equiv) in HOAc CCE = 12 mA, 40 h	> 95%	**>99/1**

*The ratios were determined by GC-MS. [a] Dibromination product also formed.

Scheme 3. Ruthenaelectro-catalyzed C–H bromination of pyrazolylarenes **3**.



Scheme 4. Gram-scale synthesis and derivatization of the bromination products.

To gain insights into the reaction mechanism, we conducted a series of experiments. Cyclic voltammetry (CV) analysis showed two oxidation peaks of HBr ($E_{p/2}=0.65$ and 1.17 V versus SCE in DMA), which are proposed to relate to the Br^-/Br_3^- and Br_3^-/Br_2 redox couples (Figure 1).[4c,19] Additional studies of the reaction mixture exhibited oxidative peaks at *ca.* $E_{p/2}=0.70$ V, suggesting that bromide anion easily undergoes anodic oxidation to generate Br_2, which equilibrates with the tribromide anion Br_3^- by combining/releasing a bromide ion under the standard conditions. In addition, when 1,3,5-trimethoxybenzene **12**, which can rapidly intercept bromine, was added into the electrochemical reaction, the *meta*-C–H bromination process was fully inhibited, generating the brominated 1,3,5-trimethoxybenzene **13** in 63 % yield (Scheme 5a). Protons were reduced at the cathode ($E_{p/2}=-0.44$ V versus SCE, Figure S10) and H_2 was observed by headspace GC analysis (see Figure S6). CV experiments showed that Br_2 was easily to be reduced at the cathode ($E_{p/2}=-0.44$ V versus SCE, Figure S10), which indicated Br_2/Br_3^- should exist in low concentration during the reaction. Indeed, addition of 1,3,5-trimethoxybenzene **12** into the standard electrochemical reaction solution (CCE = 12 mA, 3 h), cutting off the electricity and heating the mixture for another 3 h, the brominated product **13** was obtained only in 5 % yield (Scheme 5a). On-off experiment further provided strong support for this conclusion (Scheme 5b). The Br_2 produced by anodic oxidation was partially reduced at the cathode, resulting in low Faraday efficiency of the catalytic reaction.[20] In addition, the low concentration of Br_2 during the reaction might be a major cause of the high regioselectivity for the electrochemical bromination of phenylpyrazoles (Scheme 3b). To prove this, the bromination of pyrazolylarene **3a** was conducted by sequential addition of Br_2, the *meta*-C–H brominated product **4a** was obtained selectively (see Figure S4). Increasing the electric current resulted in a higher initial reaction rate (Scheme 5c), indicating that the bromination step might be the rate determining step (RDS).

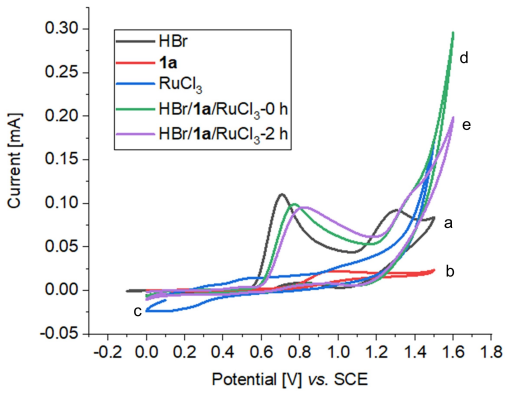
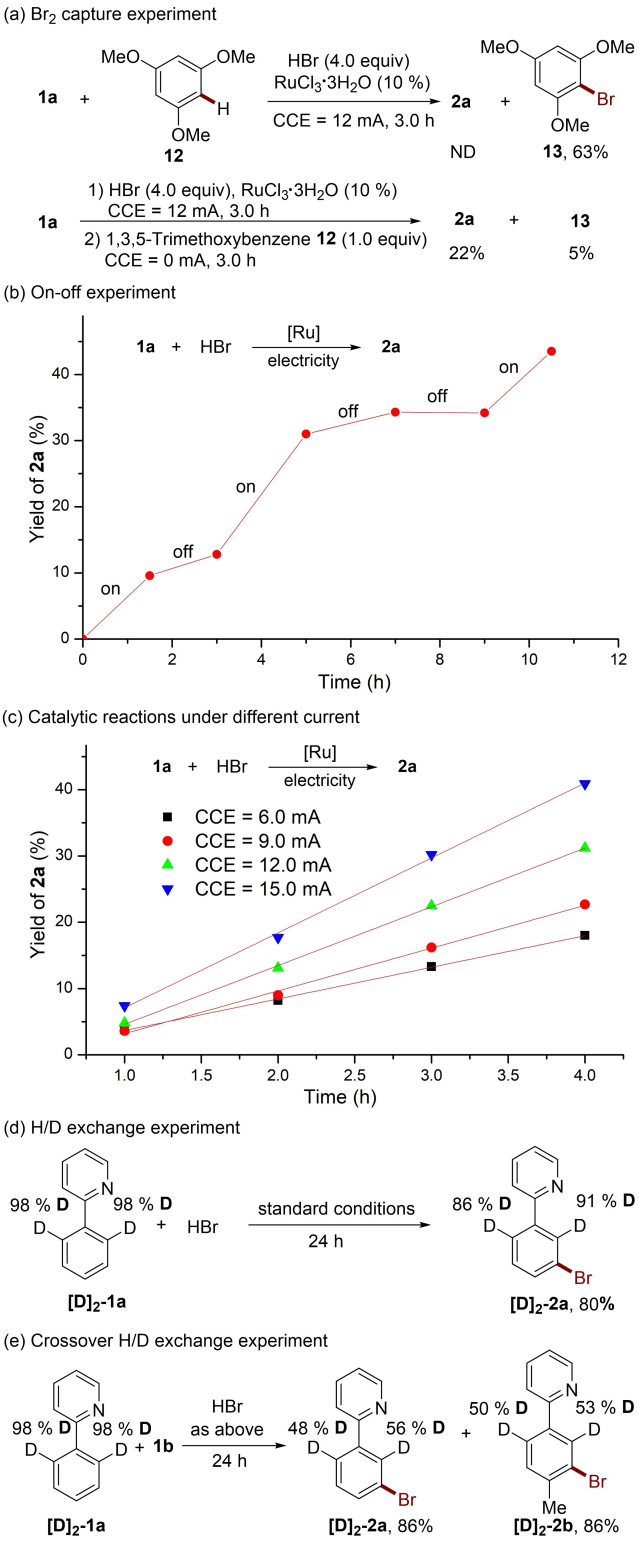


Figure 1. Cyclic voltammetry studies (DMA, 0.1 M nBu_4NPF_6, 100 mV s^{-1}). a) 10 mM HBr; b) 10 mM **1a**; c) 10 mM $RuCl_3{\cdot}3H_2O$; d) 0.5 mL of the standard reaction ($t=0$ h) solution was diluted to 10 mL with DMA; e) 0.5 mL of the reaction (CCE = 10 mA, $t=2$ h) solution was diluted to 10 mL with DMA.



Scheme 5. Summary of key mechanistic findings.

H/D exchange experiments with deuterated phenylpyridine **[D]$_2$-1a** showed only a small proportion of D loss in the brominated product (Scheme 5d). However, crossover experiment between substrates **[D]$_2$-1a** and **1b** indicated that H/D exchange occurred efficiently between different

substrates (Scheme 5e). These results suggested that ruthenacycle complex involving *ortho*-C–H activation was generated during the electrocatalysis, and protonolysis of the ruthenacycle was slow even under the acidic reaction conditions. Instead, a ligand-to-ligand hydrogen transfer (LLHT) process was considered. DFT calculations indicated that a LLHT process could readily occur via a σ-bond metathesis pathway (Figure 2).[21]

Based on our experimental results and computational results, a plausible reaction mechanism is depicted in Figure 3. The bromide ion is directly oxidized to molecular Br_2 at the anode. The ruthenium-catalyzed bromination is initiated by the formation of the cycloruthenated complex **A**.[22] Then a single-electron-transfer process occurs between **A** and Br_2 leading to intermediate **B**. Elimination of one molecule of HBr delivers intermediate **C**, which undergoes LLHT process and ligand exchange with **1a** to liberate the desired *meta*-brominated product **2a** and regenerate complex **A**. An alternative pathway involving a ruthenium (III/III) regime may also be viable at the anode (Figure S8). In addition, the S_EAr manifold between Br_2 and intermediate **A** cannot be really ruled out. Notably, though the anodic oxidation was utilized, the balanced cathodic reaction also plays key role in the undivided cell synthesis. Too high cathodic reduction potential will cause the catalyst reduction at the cathode.

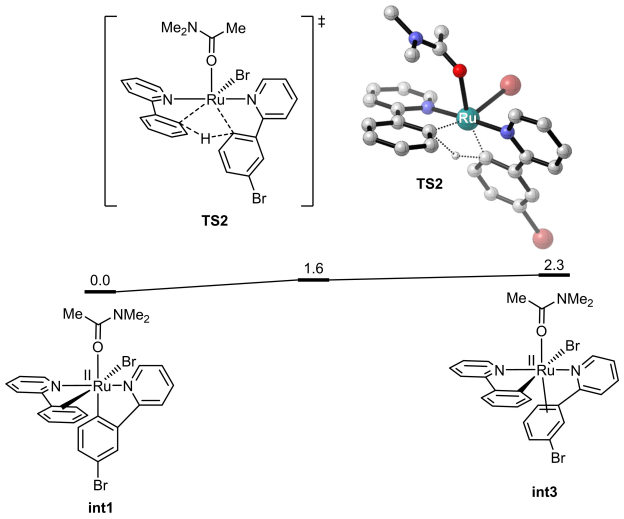


Figure 2. DFT-computed free energy changes of ligand-to-ligand hydrogen transfer via a σ-bond metathesis pathway from ruthenium (II) (**int1**). Computational methods: B3LYP-D3(BJ)/6-311+G(d,p)-SDD-SMD(n,n-Dimethylacetamide)//B3LYP-D3(BJ)/6-31G(d)-LANL2DZ.

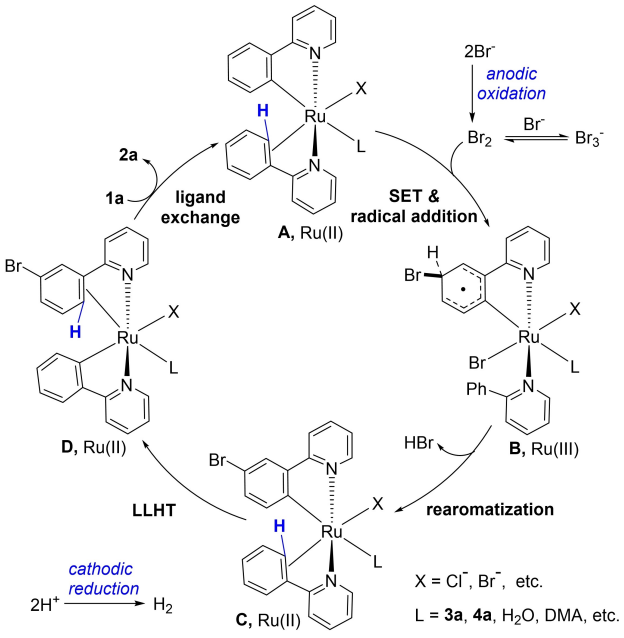


Figure 3. Proposed catalytic cycle.

Conclusion

In summary, we reported on the first electrochemical metal-catalyzed arene *meta*-C–H functionalization. The distal bromination proceeded in an undivided cell using aqueous HBr as the brominating agent under exogenous ligand- and electrolyte-free conditions. The versatility of the electrochemical remote bromination was reflected by unique regioselectivities for challenging pyrazolylarenes and gram-scale electrosynthesis. The strategy avoided the use of external chemical oxidants and provided an approach for the synthesis of versatile *meta*-substituted aryl bromide by HBr. Mechanistic studies indicated that a ruthenacycle complex is initially generated via *ortho*-C–H activation, and a LLHT process occurs to liberate the brominated product.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: C–H Activation · Electrosynthesis · Halogenations · *meta*-Functionalization · Ruthenium

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[21] Computations were performed with the Gaussian 16 software package; computational details are included in the Supporting Information. For the evaluation of possible cyclometalated ruthenium(II) species, see Figure S11 in the Supporting Information.

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