Nickel Catalyzed Electrochemical C(sp^2)−C(sp^3) Cross-Coupling Reactions

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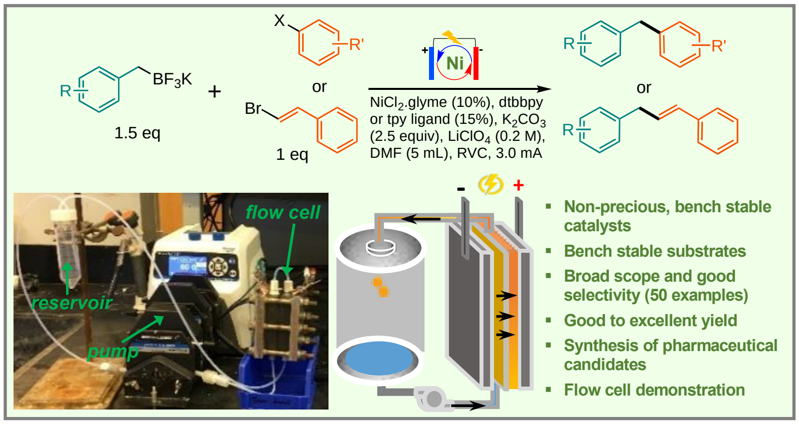

HIGHLIGHTS

- Electrochemical C(sp^2)−C(sp^3) coupling reactions are developed using bench stable, inexpensive substrates and Ni catalysts;
- The electrochemical cross-coupling exhibits broad substrate scope and good yields;
- The electrochemical cross-coupling are practical in making pharmaceutical candidates;
- Reaction scalability was demonstrated using flow cell synthesis.

The Bigger picture: Electrosynthesis has recently been recognized an enabling technology for organic synthesis. In principle, substrates or catalysts in electrosynthesis can be selectively anodically or catholically activated to participate desired reaction sequences in an electrolyzer. The attractive synthetic merits of electrosynthesis include migrating the use of reactive (sometimes even dangerous) oxidants and reductants, enabling the access of highly reactive catalytic intermediates which are not easily handled in traditional thermal reactions, and thus representing a green, atomically economical synthetic strategy. Most of reported electrosynthesis methodologies were based on an anodic or cathodic process. However, paired redox neutral electrosynthesis merging simultaneous anodic and cathodic processes remains challenging. Herein, we report a redox neutral Ni-catalyzed electrochemical C(sp^2)–C(sp^3) cross-coupling paradigm with a broad scope, good yields, and practical applications, which expands the synthetic toolbox to forge carbon-carbon bonds.

Summary: Nickel (Ni) catalyzed carbon-carbon (C−C) cross-coupling reactions haves been considerably developed in last decades and has demonstrated unique reactivities compared to palladium. However, existing Ni catalyzed cross-coupling reactions, despite success in organic synthesis, are still subject to the use of air-sensitive nucleophiles (i.e. Grignard and organozinc reagents), or catalysts (i.e. Ni^0 pre-catalysts), significantly limiting their academic and industrial adoption. Herein, we report that, through electrochemical voltammetry screening and optimization, redox neutral $C(sp^2)$–$C(sp^3)$ cross-coupling reactions can be accomplished in an undivided cell configuration using bench-stable aryl halide or β-bromostyrene (electrophiles) and benzylic trifluoroborate (nucleophiles) reactants, non-precious, bench-stable catalysts consisting of $NiCl_2$•glyme pre-catalyst and polypyridine ligands under ambient conditions. The broad reaction scope and good yields of the Ni-catalyzed electrochemical coupling reactions were confirmed by 50 examples of aryl/β-styrenyl chloride/bromide and benzylic trifluoroborates. Its potential applications were demonstrated by electrosynthesis and late-stage functionalization of pharmaceuticals, and natural amino acid modification. Furthermore, to testify practical industrial adoption, three electrochemical C−C cross-coupling reactions were demonstrated at gram-scale in a flow-cell electrolyzer. An array of chemical and electrochemical studies mechanistically indicates that the studied electrochemical C−C cross-coupling reactions proceed through an unconventional radical trans-metalation mechanism. The presented Ni-catalyzed electrochemical $C(sp^2)$–$C(sp^3)$ cross-coupling paradigm is highly productive, easily operative, and atomically economic, and is expected to find wide-spread applications in organic synthesis.

Introduction

In the past half-century, transition metal catalyzed carbon-carbon (C−C) cross-coupling reactions have gained significance advances regarding reaction scopes, selectivity, and catalytic mechanisms, and achieved tremendous success in organic synthesis of pharmaceutical molecules, agrochemicals, and organic materials.[1-3] Catalyzed C−C cross-coupling reactions have historically been dominated by Pd-based catalysts.[4-5] In addition to replacing the expensive, precious Pd metal, Ni metal is characteristic of more negative 2+/0 and 1+/0 redox potential than $Pd^{2+/0}$ to enable unique oxidative addition reactivities in activating C-X (X = Cl and Br) bonds[6] and has found increasing importance in C-C cross coupling reactions.[7-8] However, Ni catalyzed C−C cross-coupling reactions are still limited by a number of well-known synthetic limitations. Ni-based Kumda, Negish, and Suzuki, and reductive couplings are practically hampered by the use of either strong nucleophiles, sacrificed reductants, or sensitive Ni^0 pre-catalysts, e.g. widely used $Ni(COD)_2$ (where COD is 1,5-cyclooctodiene) and typically require rigid reaction conditions using inert atmosphere glovebox or Schenk-line techniques. It remains a long-standing challenge to develop Ni-catalyzed cross-coupling reactions using bench stable chemicals and easy-handling conditions for widespread academic and industrial adoption.[8] Efforts have been made to develop well-defined air stable Ni^{II} and Ni^0 pre-catalysts[9-10] and encapsulated Ni^0 pre-catalysts.[11] However, these practices are still limited by the pre-formation of Ni pre-catalysts under rigid air-free conditions and the need of special stabilization ligands for most of them.

On the other side, literature has witnessed the powerful applications of electrochemistry in organic synthesis.[12-15] By precisely controlling redox potential in an electrolyzer cell, substrates or catalysts can be selectively anodically or catholically activated to participate desired reaction sequences.[12-15] Thereby, electrosynthesis not only migrates the use of reactive (even dangerous) oxidants and reductants and enables the access of highly reactive catalytic intermediates which are not easily handled in traditional thermal reactions, representing a green, atomically economical synthetic strategy. In spite of being known for many decades, until very recently electrosynthesis has aroused recurred attention and is believed to impart profound impacts on organic syntheis.[12-15] For instance, anodic reactions including alcohol oxidation,[16] C−H functionalization,[17-24] alkene functionalization,[25-26] cyclization,[27-28] and C−O[29] and C-N[30-31] couplings, and cathodic reactions including arene or alkene hydrogenation,[32-33] and arylboronic acid hydroxylation[34] were demonstrated with good selectivity and yields. Ni-catalyzed cathodic reductive C−C homocouplings were first reported by Jennings and co-workers in 1976. Ni-catalyzed reductive cross-electrophile C−C couplings was pioneered by Jutand, Perchion and coworkers[35-37] and have been recently advanced by several groups, representing an attractive technology for C-C formation without using strong, reactive reductants as in traditional thermal reactions.[38-42] However, Ni-catalyzed redox-neutral cross couplings remain very rare,[43] in which anodic oxidation of an nucleophile and cathodic reduction of an electrophile are coupled to forge the C-C bond formation while no sacrificed stoichiometric electron donor is required. It is also worth noting that more than 97.5% of ca. 900 electrosynthesis methodologies reported between 2000 and 2017 were based on an anodic or cathodic process.[13] The development of paired redox neutral electrosynthesis has been very challenging as merging an anodic redox reaction and a cathodic redox reaction is often plagued by side reactions of reactive intermediate in each redox reaction.[13] For example, homo-coupling side-reactions can occur in electrochemical cross coupling reactions. Herein, we report that the synergic coupling of single electron transfer (SET) anodic oxidation of nucleophiles and cathodic reduction of organic halides through Ni catalysis enables efficient redox neutral electrochemical C−C cross-coupling reactions. The reported Ni catalyzed redox neutral cross-coupling reactions in this study not only hold promise to address the above-mentioned limitations of traditional Ni-catalyzed thermal coupling reactions and are also complementary to electrochemical cross-electrophile C−C couplings by expanding substrate scopes.

Results and discussion

Instead of randomly testing combinations of nucleophiles, electrophiles, and catalysts, we first set out to identify individual anodic and cathodic SET half-cell reactions for the proposed full-cell C−C coupling reactions using the electrochemical cyclic voltammetry (CV) method. For the cathodic half-cell reaction, we aimed to explore the SET reduction of $\mathrm{Ni^{II}}$-based catalysts to activate aryl and vinyl halide electrophiles by the $\mathrm{Ni^{III/I(II/0)}}$ redox cycle to achieve $\mathrm{R{-}Ni^{III(II)}{-}X}$ intermediate, which is mechanistically accessible in traditional Ni-based thermal couplings.[6] For the anodic half-reaction, nucleophiles including carboxylic acid[12] and organic trifluoroborate[44] are well documented as carbon radical precursors (R′• in Figure 1) upon SET oxidation. It is noted that organic trifluoroborates have been used as versatile radical precursors for metal photoredox catalytic coupling reactions with aryl halides by Molander and coworkers.[45] Herein, we chose potassium butyrate, pivalate, phenylacetate, butyltrifluoroborate and benzyltrifluoroborate as $\mathrm{C(sp^3)}$ sources; potassium benzoate, 3-methylcrotonate, and phenyltrifluoroborate as $\mathrm{C(sp^2)}$ sources; potassium 2-butynoate as C(sp) source (Figure 2A). The proposed concept is illustrated in Figure 1. In principle, if adopting a $\mathrm{Ni^{III/I}}$ redox cycle, a bench stable $\mathrm{Ni^{II}}$ precursor can be activated by one electron reduction using a catalytic amount of a redox active nucleophile to access the $\mathrm{R{-}Ni^{III}{-}X}$ intermediate through oxidative addition. Then after another electron reduction while a R′• radical is generated anodically, the $\mathrm{R{-}Ni^{II}{-}X}$ intermediate can trap the R′• radical to form a high-valent $\mathrm{R{-}Ni^{III}(X){-}R'}$ intermediate through single-electron transmetallation. Finally, the desired C−C cross-coupling product would be produced accompanying with the regeneration of the Ni^I catalyst through a reductive elimination reaction. The designed electrochemical C−C cross coupling reaction is (1) fundamentally attractive as a new means to forge C−C bonds, (2) practically attractive without involving reactive reactants and expensive metals, and (3) atomically economic and environmentally friendly by avoiding the use of sensitive (sometimes even dangerous) reactants or catalysts.

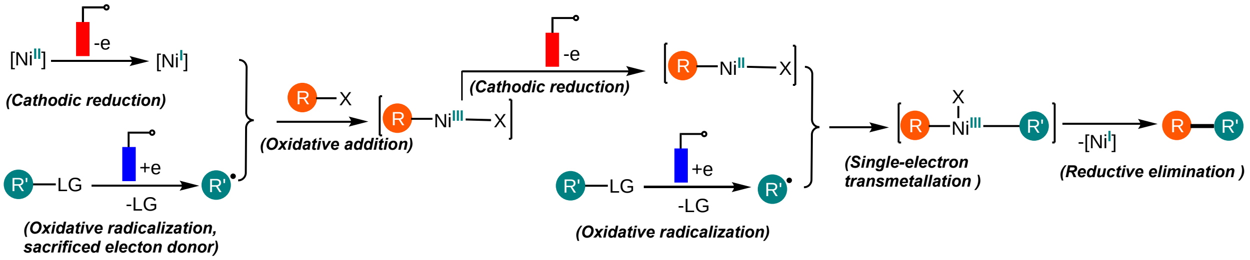

Figure 1. Designed Ni-catalyzed electrochemical C−C cross-coupling reaction. X, halides; LG, leaving groups.

Electrochemical screening of the proposed half-cell reactions was conducted through the cyclic voltammetry (CV) method using a three-electrode system. As shown in Figure 2B(i) (gray curve), in the presence of 3 equivalents 2,2'-bipyridine (2,2'-bpy) ligand, $NiCl_2$•glyme displayed a reversible redox signal at $E_{1/2} = -1.49$ V (vs. $Fc^{+/0}$), which corresponding to the $Ni^{II/I}$ redox couple. Then, 10 equivalents of organic halides (R−X) were added to the electrolyte and CV curves were collected again. Among tested organic halides, $C(sp^2)$ precursors (arly halide and alkenyl bromide) or C(sp) precursors (alkynyl bromide) could be activated by the Ni^I intermediate while $C(sp^3)$ precursors were inactive. For example, when methyl 4-bromobenzoate was added (green trace in Figure 2B(i)), the reductive peak current intensity was obviously increased, meanwhile, the return peak disappeared which indicates that an irreversible chemical reaction happened between Ni^I species and the aryl halide. The same screening experiments were conducted to the anodic substrates. As shown in Figure 2B(ii), in 0 – 1.25 V (vs. $Fc^{+/0}$) potential range, potassium benzyltrifluoroborate, phenylacetate, and pivalate displayed remarkable electrochemical reactivity with peak potential at +0.75, +0.94, and +1.02 V (vs $Fc^{+/0}$), respectively. Other substrates were electrochemically inert in the scanned potential range. Based on the CV screening results for both cathodic and anodic substrates, $C(sp^2)$ precursors (aryl halide and alkenyl bromide) or C(sp) precursors (alkynyl bromide) and $C(sp^3)$ sources (potassium benzyltrifluoroborate, phenylacetate, and pivalate) were possible combinations for electrochemical C(sp^2)−C(sp^3) or C(sp)−C(sp^3) cross-coupling reactions.

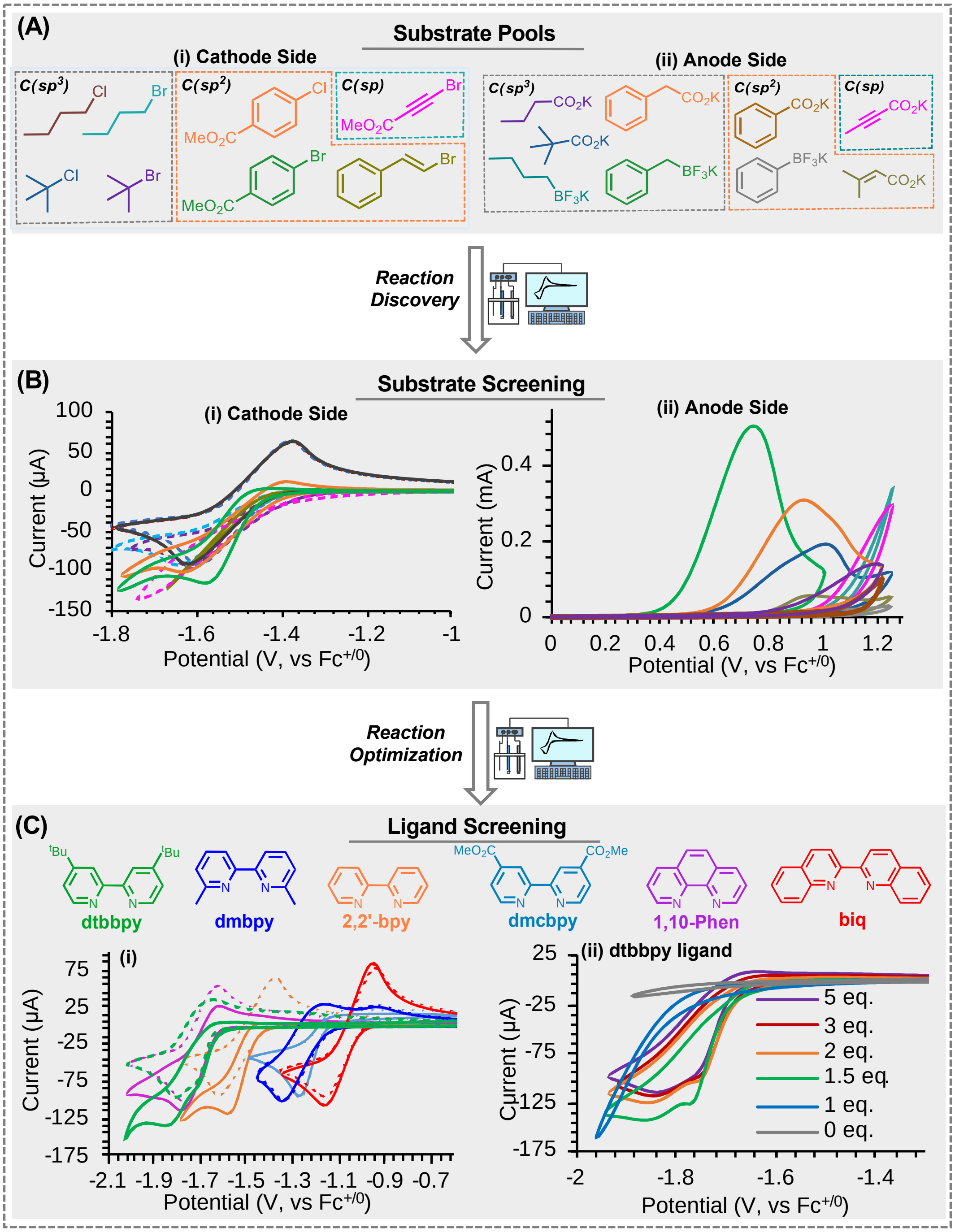

Figure 2. Electrochemical voltammetry screening of cathodic and anodic half-reactions. (A) Selected substrate pools. (B) CV screening to identify reactive substrates of cathodic (i) and anodic (ii) half-reactions. The CV curves were recorded with 5 mM $NiCl_2$.glyme, 15 mM 2,2'-bpy, and 50 mM organic halides for the cathode side screening, 0.1 M potassium trifluoroborates or

carboxylates for the anode side screening. DMF solvent, 0.2 M $LiClO_4$ supporting electrolyte, GC working electrode, 100 mV/s scan rate, room temperature. (C) CV screening of the ligand (i) and Ni/ligand ratio (ii) to optimize the cathodic half-reaction. The ligand screening curves were recorded with 5 mM $NiCl_2$.glyme and 15 mM ligand in the presence (dash line) and absence (solid line) of 50 mM methyl 4-bromobenzoate. The Ni/ligand ratio screening curves were recorded with 5 mM $NiCl_2$.glyme and 50 mM methyl 4-bromobenzoate by adding various ratio of dtbbpy ligand.

We then optimized the $NiCl_2$•glyme/polypyridine catalyst system using cyclic voltammetry with methyl 4-bromobenzoate as a model electrophile. As shown in Figure 2C(i), seven different polypyridine ligands including 4,4'-di-tert-butyl-2,2'-bipyridyl (dtbbpy), 6,6'-dimethyl-2,2'-bipyridyl (dmbpy), 2,2'-bpy, dimethyl 2,2'-bipyridine-4,4'-dicarboxylate (dmcbpy), 1,10-phenanthroline (1,10-Phen), 2,2'-biquinoline (biq), and terpyridine were screened to identify the most suitable ligand for the Ni-catalyst. Among all the ligands, dtbbpy prompted the strongest current intensity increase (green curve), indicating that $Ni^{I}(dtbbpy)^{+}$ is the most reactive species to oxidative addition of the C–Br bond of methyl 4-bromobenzoate. Besides 2,2'-bpy and dtbbpy, 1,10-Phen also aroused strong current response (purple curve) and thus can also be a suitable ligand. Terpyridine ligand displayed the lowest current response under the same conditions (Figure S5). We further investigated the effect of Ni/ligand ratio on the reactivity of the Ni-catalyst. The CV curves of $NiCl_2$•glyme with addition of various ratio of dtbbpy ligand showed continuous change (Figure S5). In the absence of the dtbbpy ligand, no reversible redox signal was observed. When 1 – 3 equivalents of dtbbpy ligand was added, there were two set of quasi-reversible redox signals. Further increase the ligand ratio to 5 equivalents, the redox signals overlapped to one set of fully reversible redox signal. It indicates that there is an equilibrium for Ni^{II} complexes in the solution: $Ni^{II} \leftrightarrow Ni^{II}(dtbbpy) \leftrightarrow Ni^{II}(dtbbpy)_2 \leftrightarrow Ni^{II}(dtbbpy)_3$, which is consistent with a previous UV-Vis study.[30] In the presence of methyl 4-bromobenzoate substrate, the addition of 1.5 equivalent of dtbbpy ligand (Figure 2C(ii), green curve) yielded the highest cathodic current. Adding more ligand (2 – 5 equivalents), the reductive peak current intensity slightly decreased, and the return peak gradually showed up, which is most likely due to the decreased reactivity of Ni-catalyst after coordination to multiple dtbbpy ligands ($Ni(dtbbpy)_2$ and $Ni(dtbbpy)_3$).

Encouraged by the positive observations in the electrochemical voltammetry studies, we proceeded to test the $C(sp^2)$–$C(sp^3)$ cross-coupling full-reaction by combining the oxidative radicalization of benzylic trifluoroborates and Ni-catalyzed C−X activation of aryl halides in an undivided cell. A starting electrolysis system consisting of $NiCl_2$•glyme catalyst, dtbbpy ligand, and $LiClO_4$ supporting electrolyte confirmed the cross-coupling of methyl 4-bromobenzoate and potassium benzyltrifluoroborate in 47% yield (produce methyl 4-benzylbenzoate, **1**) after galvanostatic electrolysis at 3.0 mA for 28 h. Dimethyl 4,4'-biphenyldicarboxylate (**1'**) from the homo-coupling of methyl 4-bromobenzoate was isolated as the main by-product in 38% yield. To further improve the reaction yield, a number of supporting electrolytes ($TBAPF_6$, KPF_6, and $NaBF_4$) and salt additives (K_2CO_3, Na_2CO_3, and KOAc) were tested to optimize the reaction efficiency (Table S1). It was found that the yield for **1** was further improved to 93% using K_2CO_3 additive. The essentiality of $NiCl_2$•glyme catalyst, dtbbpy ligand, and electrolysis was determined by control experiments (Table S1, SI). In addition, both reaction selectivity and rate were largely affected by current intensity. Lower selectivity was obtained under a higher or lower current intensity (64% under 1.0 mA, 77% under 5.0 mA current). Under 1.0 mA current electrolysis, the reaction was significantly decelerated as a reaction time of 48 h needs to fully convert the substrate. Other solvents, such as THF, MeCN, CH_2Cl_2, MeOH, and DMSO were not effective to this reaction (only 0 – 15% yield was observed, Table S2, SI). Moreover, similar as under thermal reaction conditions,[16] the reactivity and selectivity of this reaction is highly sensitive to the ligand structure (Table S3, SI). In particular, dtbbpy and 2,2'-bpy ligands exhibited the best efficiencies with isolated yields of 93% and 87%, respectively. 1,10-Phen and tridentate terpyridine (tpy) ligands gave moderate yields of 67% and 73%, respectively. It is noteworthy that the best selectivity between cross-coupling product **1** and homo-coupling product **1'** was obtained by using the dtbbpy (95:5) and tpy (96:4) ligands, which tend to suppress the homo-coupling of strong electrophiles. However, other ligands (dmbpy, dmcbpy, and biq) were not effective. Moreover, no product was observed when a bidentate bis-phosphine ligand, 1,2-bis(diphenylphosphino)benzene (dppb) was used (Table S3). It was observed that the dppb ligand underwent oxidation near to the oxidation potential of benzyltrifluoroborate, which could destabilize the corresponding Ni catalyst (Figures S6 and S7).

After establishing optimal reaction conditions for yield and selectivity for the Ni-catalyzed electrochemical $C(sp^2)$–$C(sp^3)$ cross-coupling, we next tested the reaction scope on both aryl halide and benzylic trifluoroborate using the most efficient Ni/dtbbpy catalyst. As shown in Figure 3, a wide range of aryl chlorides including both electron-rich and electron-deficient arenes were suitable to this Ni-catalyzed electrosynthesis system (**1** to **5**). The electron-deficient aryl chlorides (**1** to **3**, 74% to 86% yield) delivered better yield than the electron-rich ones (**4** and **5**, 46% and 31% yield). It is probably due to the low activity of electron-rich aryl chloride substrates with the Ni^I intermediate. Aryl bromides displayed better efficiencies than the corresponding aryl chlorides, as **1** to **5** were isolated in 77% to 93% yield by using aryl bromide substrates. The reaction exhibited comparable efficiency upon scale-up, for example, 89% yield was obtained on a 2.5 mmol scale reaction of **1** (0.5 g). The substituent position of aryl bromide displayed a moderate effect to the reaction efficiency, as the para-, meta- and ortho-substituted methyl bromobenzoate delivered 93%, 71%, and 89% yield (**1**, **6** and **7**), respectively. Aryl bromides with functional groups as diverse as ester (**1**, **6**, **7**, and **10**), ketone (**2**), fluoride (**3**), methoxy group (**9** and **10**), amide (**14** and **15**), aldehyde (**11**), nitrile (**12**) and alkenyl (**19**) were effective in this reaction. Substrates possessing strongly electron-donating substituents such as ^{t}Bu and methoxy groups could also provide moderate to good yield (72% for **8** and 53% for **9**). When 4-bromo-phenol was used as the electrophile as a control experiment for entry **9**, no cross-coupling product was observed, which is attributed to the oxidation of the substrate itself at a less positive potential than the borate nucleophile. The observation emphasizes the protection of oxidization susceptible functional groups under the investigated electrochemical conditions. It is interesting that for the substrates possessing strong electron-withdrawing substituents such as aldehyde, acetyl, and cyano groups, best results were obtained by using 2,2'-bpy ligand (83% and 91% yield for **2** from chloride and bromide, respectively, 82% yield for **11**, and 74% yield for **12**). Furthermore, in the case of 4-bromo(trifluoromethyl)benzene, homo-coupling product, 4,4'-bis-(trifluoromethyl)biphenyl (**13'**), was obtained as the only product when using dtbbpy and 2'2-bpy ligands. Interestingly, 21% yield of cross-coupling product **13** was obtained by using the tpy ligand, implying the Ni/tpy ligand combination is more compatible with electron deficient electrophiles to suppress homo-coupling.

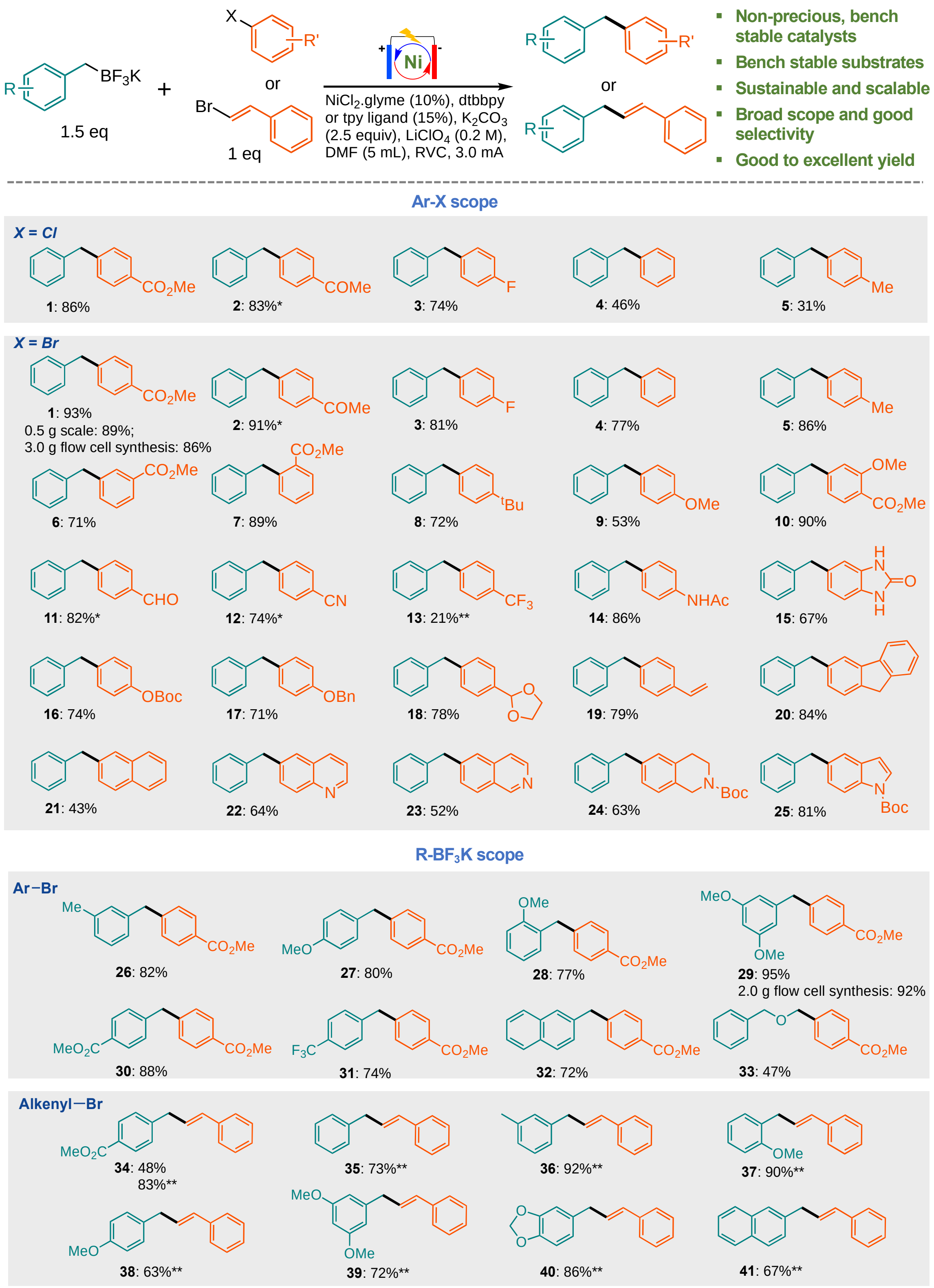

Figure 3. Substrate scope of the Ni-catalyzed electrochemical C(sp^2)–C(sp^3) cross-coupling reaction. Yields refer to isolated yields of products after chromatography on silica gel. Standard

conditions: aryl halide or β-bromostyrene substrate (0.5 mmol), trifluoroborate substrate (0.75 mmol), $NiCl_2$.glyme (50 µmol), dtbbpy ligand (75 µmol), K_2CO_3 (1.25 mmol), $LiClO_4$ (0.2 M), DMF (5 mL), RVC as anode and cathode, 3 mA current electrolysis under Ar at room temperature for 20 – 36 h. *75 µmol 2,2'-bppy as ligand. **50 µmol tpy as ligand. In case of **13**, an inseparable mixture of **13** and **13'** was obtained, 41% purity.

In addition to examine the substituent positions and functional groups of the aryl halide substrates, we also investigated the tolerance of this electrosynthesis system to common protecting groups which are widely used in organic synthesis, such as amide, tert-butyloxycarbonyl (Boc), benzyl ether (BnO), and acetal. All of these protecting groups were well tolerated, as evidenced by good isolation yield of **14** to **18** (67% to 86% yield). The π-conjugation extended aryl bromide substrates including 4-bromophenylethene, 3-bromofluorene, and 2-bromonaphthalene also smoothly proceeded this cross-coupling reaction with moderate to good yield (**19** to **21**, 43% to 84% yield). Moreover, a variety of aryl bromides consisting of nitrogen-containing heterocyclic groups including 6-bromoquinoline, 6-bromoisoquinoline, and Boc protected 6-bromotetrahydroisoquinoline, and 5-bromoindole, which are prevalent building blocks in bio-active molecules, delivered moderate to good yield (**22** to **25**, 52% to 81% yield).

The substrate scope of benzylic trifluoroborate salts was also investigated. As shown in Figure 3, both electron-rich and electron-deficient benzylic trifluoroborates were approved efficient carbon radial precursors in this cross-coupling reaction (**26** to **31**, 74% to 95% yield). Functional groups, including esters, methoxy group, and trifluoromethyl group were tolerant to this Ni-catalyzed electrosynthesis. The substituent positions displayed negligible effects to the reaction efficiency, as comparable yield was obtained for the para-, meta-, and ortho-substituted benzylic trifluoroborates (**26** to **28**, 77% to 82% yield). In the presence of two strong electron-donating methoxy (MeO-) groups, the highest yield, 95%, was gained for **29,** which is interpreted as the favorable oxidation kinetics of the corresponding trifluoroborate substrate. The π-conjugation extended naphthalen-2-ylmethyl trifluoroborate is also highly productive in this electrochemical $C(sp^2)–C(sp^3)$ cross-coupling reaction, as 72% yield was obtained for **32**. Beside the benzylic trifluoroborates, (benzyloxy)methyl trifluoroborate also manifested reasonable reactivity in this reaction with a yield of 47% (**33**).

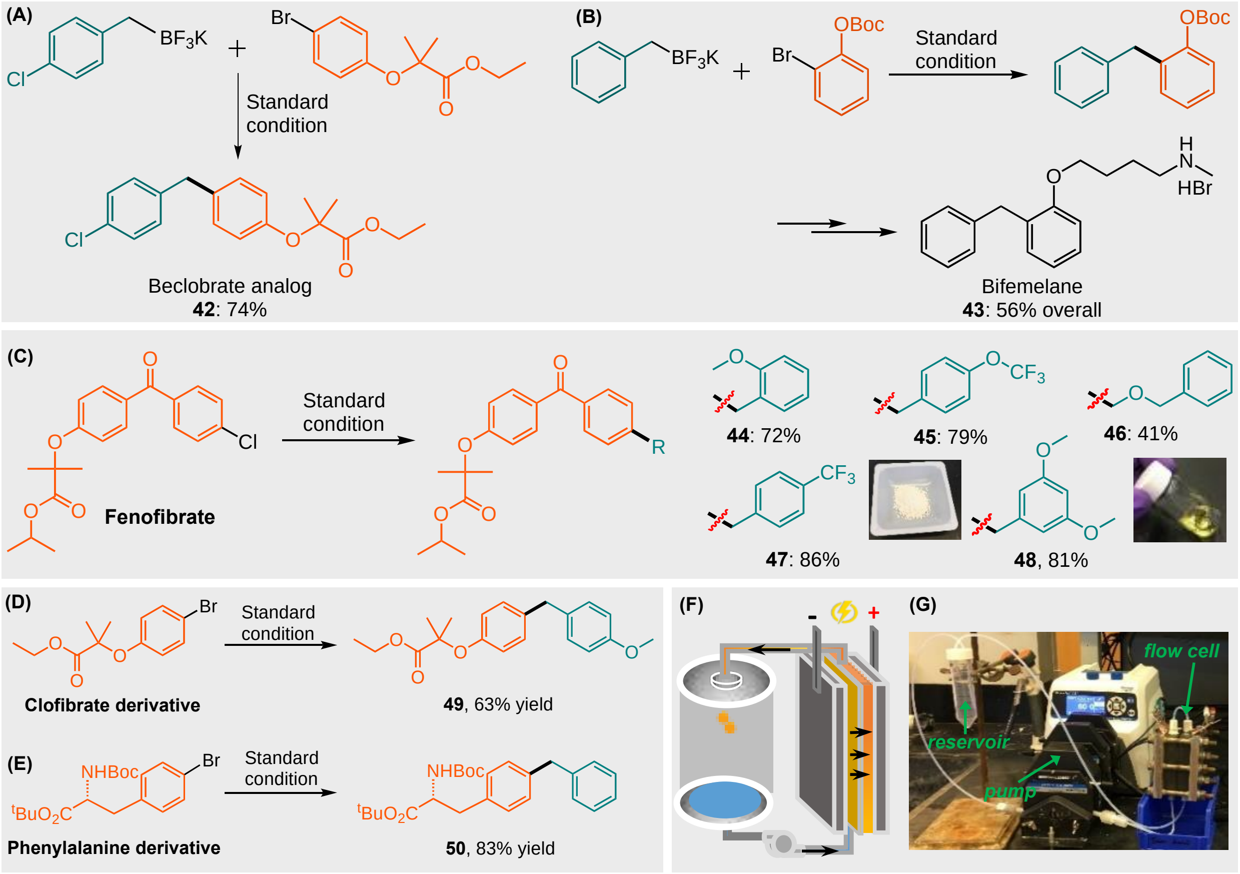

Figure 4. Applications of the Ni-catalyzed electrochemical C(sp^2)–C(sp^3) cross-coupling reaction. Electrosynthesis of pharmaceutical molecules Beclobrate analog (A) and Bifemelane (B). Late-stage functionalization of Fenofibrate (C), Clofibrate derivative (D), and modification of brominated phenylalanine (E). (F) schematic drawing and (G) experimental setup of the electrosynthesis flow-cell. Yields refer to isolated yields of products after chromatography on silica gel.

In the CV screening studies (Figure 2B), some other substrates also showed reactivity in the anodic half-reaction. For example, β-bromostyrene and methyl 3-bromopropiolate showed reactivity in the anodic half-cell reaction (Figure S4, SI). β-bromostyrene was briefly examined as an electrophile for the Heck-type like C(sp^2)–C(sp^3) cross-coupling. In the reaction of β-bromostyrene and potassium trifluoro(4-(methoxycarbonyl)benzyl)borate, 48% yield of product **34** and 47% yield of the homo-coupling product **34’** were obtained by using dtbbpy as ligand. According to entry **13**, the tpy ligand exhibited the better selectivity to suppress the homo-coupling product. Then the coupling reaction using β-bromostyrene was optimized with the typ ligand. The improved yield and selectivity for the cross-coupling product **34** were obtained in the presence of the tpy ligand (83% yield, 90% selectivity) (Table S4, SI). As shown in Figure 3, both electron-rich and electron-deficient benzylic trifluoroborates were efficient in this cross-coupling reaction (**34** to **40**, 63% to 92% yield). Functional groups including esters, methoxy group, and benzodioxol group were tolerant in this Ni-catalyzed electrochemical reaction. The π-conjugation extended naphthalen-2-ylmethyl trifluoroborate also provided good reactivity in this reaction, as 67% yield was obtained for **41**. However, other anodic nucleophiles (3-bromopropiolate, phenylacetic acid, potassium pivalate, and potassium phenyltrifluoroborate) didn't provide satisfactory results (see Figure S9 and the SI for more discussions).

To demonstrate potential applications of this Ni-catalyzed electrochemical C(sp^2)–C(sp^3) cross-coupling methodology, we first exploited the synthesis of pharmaceutical molecules containing the diphenylmethane structural component. Beclobrate analog (**42**, a hypolipidemic candidate[46]) and Bifemelane (**43**, an antidepressant candidate[47]) were synthesized with 74% and 56% overall yield, respectively (Figure 4A and 4B). We further utilized this methodology in late-stage functionalization of pharmaceuticals which is a popular way for fast discovery of new drag candidates. Fenofibrate is a pharmaceutical molecule of the fibrate class and used to treat abnormal blood lipid levels.[48] As shown in Figure 4C, Fenofibrate was successfully converted to a series of brand-new compounds (**44** to **48**, 41% to 86% yield) in up to 2.5 mmol (0.93 g) scale form a regular vial electrolyzer cell. Another new Clofibrate derivative (a lipid-lowering agent) was synthesized using this electrochemical approach (**49**, 63% yield) (Figure 4D). In addition, the electrochemical C−C cross-coupling reaction was also effective in modification of brominated natural amino acids, e.g. phenylalanine, (Figure 4E) (**50**, 83% yield). To further testify the potential industrial adoption of the present electrochemical cross-coupling reaction, flow cell synthesis (Figure 4F and 4G) was demonstrated with compounds **1**, **29** and **48** with a reaction scale greater than 2.0 g. It should be noted reaction solutions were only flushed with nitrogen gas in the flow cell synthesis without using rigid glovebox or Schlenk-line techniques. Under the flow-cell condition, all three compounds were obtained with good to excellent yields (86% for **1** at 3.0 g scale, 92% for **29** at 2.0 g scale, and 84% for **48** at 3.0 g scale).

To gain mechanistic understandings of this Ni-catalyzed electrochemical C(sp^2)–C(sp^3) cross-coupling reaction, a radical-trapping experiment was conducted for the anodic half-reaction.

As shown in Figure 5A, controlled potential electrolysis (at 1.2 V, vs. $Fc^{+/0}$) of the potassium trifluoro(4-(methoxycarbonyl)benzyl)borate and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) in a divided-cell produced radical coupling product **51** with 86% isolated yield, which confirms the formation of 4-(methoxycarbonyl)benzyl free radical in the anodic oxidation process. In addition, plots of overpotential over the logarithm of kinetic current and the corresponding fitted Tafel plots were constructed to determine charge transfer rate constants (k^0) of potassium benzyltrifluoroborate and phenylacetic acid in the presence of 2.5 equiv Cs_2CO_3 in the anodic oxidation process (Figure 5B and see the SI for detail). k^0 of potassium benzyltrifluoroborate and cesium phenylacetate were calculated as 5.56 x 10^{-5} cm/s and 1.39 x 10^{-5} cm/s, respectively. The higher charge transfer rate constant of potassium benzyltrifluoroborate indicates faster electrochemical reactivity to generate carbon radicals than cesium phenylacetate, which is consistent with the better efficiency of potassium benzyltrifluoroborate in the cross-coupling reaction than cesium phenylacetate (30% yield). It is believed that the quick formation of the carbon radical is critical to trap the R-Ni^{II}-X intermediate, otherwise the R-Ni^{II}-X intermediate can promote the homo-coupling side reaction.

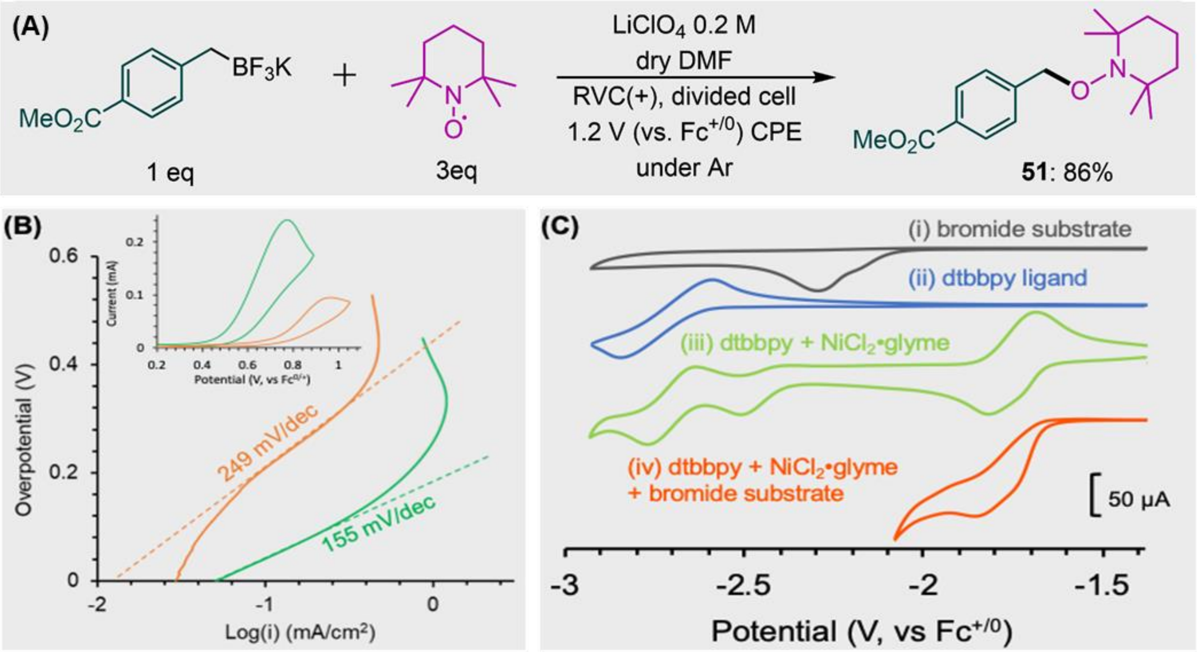

Figure 5. Reaction mechanism studies of the Ni-catalyzed electrosynthesis system. (A) Carbon free radical trapping reaction. (B) Plots of overpotential over the logarithm of kinetic current and the fitted Tafel plots of phenyl trifluoroborate (green) and cesium phenylacetate (orange). Inset: CV curves of potassium phenyl trifluoroborate (green) and cesium phenylacetate (orange);

conditions: 10 mM in DMF, $LiClO_4$ (0.2 M) supporting electrolyte, GC working electrode, and 100 mV/s scan rate. **(**C**)** CV curves of 50 mM methyl 4-bromobenzoate (gray), 15 mM dtbbpy ligand (blue), 5 mM $NiCl_2$•glyme + 25 mM dtbbpy (green), and 5 mM $NiCl_2$•glyme + 15 mM dtbbpy + 50 mM methyl 4-bromobenzoate (orange) in DMF with 0.2 M $LiClO_4$ supporting electrolyte.

Electrochemical studies were conducted to gain additional mechanistic insights for the cathodic process. As shown in Figure 5B, methyl 4-bromobenzoate substrate displayed irreversible redox signal with onset potential at -2.05 V (vs $Fc^{+/0}$) and dtbbpy ligand delivered reversible redox signal with $E_{1/2}$ = -2.70 V (vs. $Fc^{+/0}$), respectively. The mixture of $NiCl_2$•glyme and 1.5 equiv dtbbpy ligand exhibits three redox peaks at $E_{1/2}$ = -1.74 V, -2.44 V, and -2.70 V (vs. $Fc^{+/0}$), which corresponding to $Ni^{II/I}$, $Ni^{I/0}$ redox couples, and the free ligand. When the methyl 4-bromobenzoate substrate was added, significant increase of reductive current and disappearance of the return peak was observed for the $Ni^{II/I}$ redox couples. It indicates that the Ni^{I} is the reactive species for the oxidative addition of aryl halide. In addition, CV curves of the reaction mixture displayed -1.60 V and 0.33 V (vs. $Fc^{+/0}$) onset potentials for cathodic and anodic half-reactions, respectively (Figure S10). The potential of cathode was retained between -1.7 and -1.9 V (vs. $Fc^{+/0}$) during the reaction (Figure S11), and the observation further indicates that the $Ni^{I/0}$ redox couple is not involved in the cathodic process.

Based on the chemical and electrochemical studies, a possible reaction mechanism for this Ni-catalyzed electrochemical $C(sp^2)$–$C(sp^3)$ cross-coupling is proposed and illustrated in Figure 6. The reaction is initiated by the electrochemical reduction of Ni^{II} catalyst **A** to Ni^{I} species **B**, the latter further oxidative addition to aryl halide substrate **C** to generate an Ar–Ni^{III} complex **D**. **D** is subsequently electrochemically reduced to Ar–Ni^{II} species **E**. Simultaneously, a benzylic carbon free radical **G** generated through oxidative degradation of benzylic trifluoroborate or phenylacetate substrate **F** in the anode side is captured by **E** to form a high-valent Ar–Ni^{III}–Bn species **H**. Then, **H** undergoes reductive elimination to produce the cross-coupling product **I** and recover the Ni^{I} catalyst **B**. Compared to the reported photocatalytic cross coupling of benzoic trifluoroborates and aryl halides by Molander and coworkers,[45] which relies on an iridium photocatalyst to activate trifluoroborates and regenerate a Ni^{0} catalyst, the key mechanistic difference of the present electrochemical coupling is that both the reactive carbon radical and Ni^{I} intermediate are generated electrochemically. Without using the expensive iridium photocatalyst and the reactive Ni^0 catalyst, the present electrochemical cross coupling is more affordable, scalable, and practical. Molander's photocatalytic cross coupling is also capable of using alkyl trifluoroborate nucleophiles as radical precurors.[49] Nevertheless, this electrochemical cross-coupling protocol is not effective to handle reactive alkyl radicals. Through optimization of reaction conditions and catalysts, it is likely to expand the scope of nucleophiles to alkyl and phenyl trifluoroborates, and even carboxylic acids for electrochemical cross coupling.

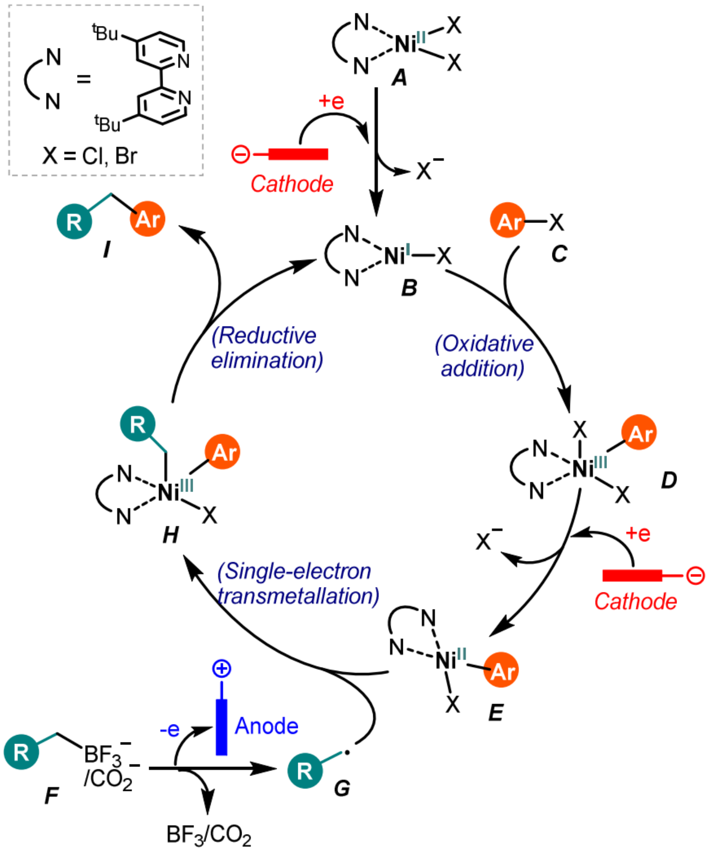

Figure 6. Proposed reaction mechanism for the Ni-catalyzed electrochemical $C(sp^2)$–$C(sp^3)$ cross-coupling reaction.

Conclusions

In summary, a Ni-catalyzed electrochemical cross-coupling methodology was developed to forge the $C(sp^2)$–$C(sp^3)$ bond with broad substrate scope, excellent functional group tolerance, selectivity, and good yields. In addition, the cyclic voltammetry proved an effective and efficient way for the discovery, optimization, and mechanistic understanding of anodic and cathodic half-reactions and can be used as a go-to method for developing other useful electrosynthesis methodologies. Compared to traditional thermal Ni catalyzed cross-coupling reactions, the present electrochemical approach is advantageous as all reactants and catalysts are bench stable without using reactive oxidants/reductants and complex inert atmosphere techniques. As exemplified in gram-scale synthesis in the flow-cell synthesis and the late-stage functionalization of pharmaceuticals, this electrochemical C−C coupling methodology is expected to be widely applied to the construction of C(sp^2)–C(sp^3) bonds in developing pharmaceutical molecules, agrochemicals, and organic materials. The Ni-catalyzed electrochemical C-C cross coupling reactions can be further advanced for broader substrates and extended to other types of coupling reactions. Moreover, the present new C-C bond formation paradigm (and also extended reactions) can offer rich opportunities to pursue fundamental mechanistic studies and thus lead to the discovery of new catalytic knowledge at the interface of synthetic chemistry and electrochemistry.

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Conflicts of Interest

A patent application including the submitted results was filed.

Supplementary Information provides experimental details, supporting figures, and supporting tables.

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