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Nickel Catalyzed Electrochemical C(sp³)–C(sp²) Cross-Coupling Reactions of Benzyl Trifluoroborate and Organic Halide

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Abstract: Herein, we report redox neutral electrochemical C(sp²)-C(sp³) cross-coupling reactions of bench-stable aryl halide or βbromostyrene (electrophiles) and benzylic trifluoroborate (nucleophiles) using non-precious, bench-stable NiCl₂•glyme/polypyridine catalysts in an undivided cell configuration 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 electrosynthesis and late-stage functionalization by 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 flowcell electrolyzer. An array of chemical and electrochemical studies mechanistically indicates that the studied electrochemical C-C crosscoupling reactions proceed through an unconventional radical transmetalation mechanism. The presented Ni-catalyzed electrochemical C(sp²)-C(sp³) cross-coupling paradigm is highly productive and expected to find wide-spread applications in organic synthesis.

Introduction

In the past half-century, transition metal catalyzed carboncarbon (C-C) cross-coupling reactions have gained significant advances regarding reaction scopes, selectivity, and catalytic mechanisms, and have achieved tremendous success in organic synthesis of pharmaceutical molecules, agrochemicals, and organic materials.^[1-3] Historically, catalyzed C-C cross-coupling reactions have 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 = CI and Br) bonds and has found increasing importance in C-C cross coupling reactions.^[6] 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 hampered by the use of either strong nucleophiles, sacrificial reductants, or sensitive Ni⁰ pre-catalysts, e.g. widely used Ni(COD)₂ (where COD is 1,5-cyclooctodiene) typically require rigid reaction conditions using an inert atmosphere glovebox or Schenk-line techniques. The long-standing challenge remains to develop Nicatalyzed cross-coupling reactions using bench stable chemicals and easy handling conditions for widespread academic and

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

industrial adoption.^[7] It is worth noting that recent success in dual Ni/photoredox catalyzed cross-coupling reactions has opened novel catalytic routes to advance traditional thermal Ni catalyzed cross-coupling reactions.^[8, 9]

On the other hand, the existing literature is evidence of the powerful applications of electrochemistry in organic synthesis.^{[10-} ^{13]} By precisely controlling redox potential in an electrolyzer cell, substrates or catalysts can be selectively anodically or cathodically activated to produce desired reaction sequences.[10-^{13]} Thereby, electrosynthesis not only migrate the use of reactive (even dangerous) oxidants and reductants, it enables 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 around for many decades, electrosynthesis has recently aroused attention as it is believed to have profound impacts on organic synthesis.^[10-13] For instance, anodic reactions including alcohol oxidation,^[14] C-H functionalization,^[15-22] alkene functionalization, $^{[23,\ 24]}$ cyclization, $^{[25,\ 26]}$ and C-O $^{[27]},\ C-N ^{[28,\ 29]}$, and C-P^[30-32] couplings, and cathodic reactions including arene or alkene hydrogenation,^[33, 34] and arylboronic acid hydroxylation^[35] have demonstrated good selectivity and yields. Ni-catalyzed cathodic reductive C-C homocouplings were first reported by Jennings and co-workers in 1976. Ni-catalyzed reductive crosselectrophile C-C couplings were pioneered by Jutand, Perchion and coworkers^[36-38] and recently have been advanced by several groups, representing an attractive technology for C-C formation without using strong, reactive reductants as in traditional thermal reactions.[39-43]

However, Ni-catalyzed redox-neutral cross couplings in which anodic oxidation of a nucleophile and cathodic reduction of an electrophile are coupled to forge the C-C bond formation while no sacrificed stoichiometric electron donor is required, remain very rare,^[44, 45] 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.[11] Recent effort has been made to develop paired redox-neutral Ni-catalyzed electrosynthesis for C-N, C-S, and C-O bond coupling reactions.[46-48] 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 intermediates in each redox reaction.[11] 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 for addressing the above-mentioned limitations of traditional Ni-catalyzed thermal coupling reactions but are also

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

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 fullcell 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 Ni^{II}-based catalysts to activate aryl and vinyl halide electrophiles by the Ni^{III/I(II/0)} redox to achieve R-Ni^{III(II)}-X intermediate, which cycle is mechanistically accessible in traditional Ni-based thermal couplings.^[6, 7] For the anodic half-reaction, nucleophiles including carboxylic acid^[10] and organic trifluoroborate^[49] 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.^[8] Herein, we chose potassium butyrate, pivalate, phenylacetate, butyltrifluoroborate and benzyltrifluoroborate as C(sp³) sources; potassium benzoate. 3-methylcrotonate, and phenyltrifluoroborate as C(sp²) sources; potassium 2-butynoate as C(sp) source (Figure 2A). The proposed concept is illustrated in Figure 1. In principle, if adopting a Ni^{III/I} redox cycle, a bench stable Ni^{II} precursor can be activated by one electron reduction using a catalytic amount of a redox active nucleophile to access the R-Ni^{III}-X intermediate through oxidative addition. Then, after another electron reduction while a R' radical is generated anodically, the R-Ni^{II}-X intermediate can trap the R' radical to form a high-valent R-Ni^{III}(X)-R' intermediate through singleelectron 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.

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, NiCl₂•glyme displayed a reversible redox signal at $E_{1/2} = -1.49$ V (vs. Fc^{+/0}), which corresponds 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(sp²) precursors (aryl halide and alkenyl bromide) or C(sp) precursors (alkynyl bromide) could be activated by the Ni¹ intermediate while C(sp³) 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 Niⁱ 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(sp²) precursors (aryl halide and alkenyl bromide) or C(sp) precursors (alkynyl bromide) and C(sp³) sources (potassium benzyltrifluoroborate, phenylacetate, and pivalate) were possible combinations for electrochemical C(sp²)-C(sp³) or C(sp)-C(sp³) cross-coupling reactions.

We then optimized the NiCl₂•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 reactive species for oxidative addition of the C-Br bond of methyl 4bromobenzoate. 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 NiCl₂•glyme with the 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

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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 5.0 mM NiCl₂.glyme, 15.0 mM 2,2'-bpy, and 50.0 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 LiClO₄ 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 5.0 mM NiCl₂.glyme and 50 mM methyl 4-bromobenzoate. The Ni/ligand ratio screening curves were recorded with 5.0 mM NiCl₂.glyme and 50 mM methyl 4-bromobenzoate by adding various ratio of dtbbpy ligand.

were added, there were two sets of quasi-reversible redox signals. With a further increase of the ligand ratio to 5 equivalents, the redox signals overlapped to one set of fully reversible redox signal. This 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.^[28] 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

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Table	1. Optimization for the Ni-cataly	e Ni-catalyzed electrochemical C(sp ²)–C(sp ³) cross-coupling reactions.			
BF		Standard conditions		CO ₂ Me	
1.5 eq	1 eq		MeO ₂ C		
Entry	Variation from standard conditions ^[a]	Conversion (%) ^[b]	Yield of 1 (%) ^[c]	Yield of 1' (%) ^[c]	
1	None ^[d]	100	93	5	
2	No dtbbpy ligand	0	0	0	
3	No NiCl ₂ .glyme	0	0	0	
4	Na ₂ CO ₃ instead of K ₂ CO ₃	100 (48 h)	78	15	
5	KOAc instead of K ₂ CO ₃	100	0	86	
7	No K ₂ CO ₃	100	47	38	
8	TBAPF ₆ instead of LiClO ₄	100 (20 h)	74	16	
9	KPF ₆ instead of LiClO ₄	100 (22 h)	89	9	
10	NaBF ₄ instead of LiClO ₄	100 (20 h)	75	20	
11	No current	0	0	0	
12	1.0 mA current electrolysis ^[d]	100 (48 h)	48	27	
13	5.0 mA current electrolysis ^[d]	100	76	23	

[a] Standard conditions: methyl 4-bromobenzoate (108 mg, 0.5 mmol, 1.0 eq.), potassium benzyl trifluoroborate (149 mg, 0.75 mmol, 1.5 eq.), NiCl₂.glyme (11 mg, 50 µmol, 10 mol%), dtbbpy (20 mg, 75 µmol, 15 mol%), K₂CO₃ (173 mg, 1.25 mmol, 2.5 eq.), LiClO₄ (106 mg, 0.2 M), DMF (5 mL), RVC as anode and cathode, 3.0 mA current under Ar at room temperature for 28 h. [b] Conversion was measured by ¹H-NMR using 4-bromobenzaldehyde as internal standard. [c] Isolated yield.

peak gradually showed up, which is most likely due to the decreased reactivity of Ni-catalyst after coordination with 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(sp²)–C(sp³) cross-coupling full-reaction by combining the oxidative radicalization of benzylic trifluoroborates and Nicatalyzed C-X activation of aryl halides in an undivided cell. An initial electrolysis system consisting of NiCl₂•glyme catalyst, dtbbpy ligand, and LiClO₄ -supporting electrolyte confirmed the cross-coupling of methyl 4-bromobenzoate and potassium benzyltrifluoroborate in 47% yield (produce methyl 4benzylbenzoate, 1) after galvanostatic electrolysis at 3.0 mA for 28 h (entry 7 in Table 1). 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 (TBAPF₆, KPF₆, and NaBF₄) and salt additives (K₂CO₃, Na₂CO₃, and KOAc) were tested to optimize the reaction efficiency (Table 1). It was found that the yield for 1 was further improved to 93% using K₂CO₃ additive. The essentiality of NiCl₂•glyme catalyst, dtbbpy ligand, and electrolysis was determined by control experiments (Table 1). In addition, both reaction selectivity (ratio between 1 and 1') 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 was needed to fully convert the substrate (entry 6, Table 1). Other solvents, such as THF, MeCN, CH₂Cl₂, MeOH, and DMSO were not effective for this reaction (only 0 -15% yield was observed, Table S1, SI). Similarly, under thermal reaction conditions,¹⁶ the reactivity and selectivity of this reaction is highly sensitive to the ligand structure (Table S2, 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 vields of 77% 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 (93% : 5%) and tpy (73%: 3%) ligands, which tend to suppress the homo-coupling of strong electrophiles. However, other ligands (dmbpy, dmcbpy, and biq) were not effective. Moreover, no cross-couping product was observed when a bidentate bis-phosphine ligand, 1,2bis(diphenylphosphino)benzene (dppb) was used (Table S2, SI). It was observed that the dppb ligand underwent oxidation near the oxidation potential of benzyltrifluoroborate, which could destabilize the corresponding Ni catalyst (Figures S8, SI).

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

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Figure 3. Substrate scope of the Ni-catalyzed electrochemical $C(sp^2)$ – $C(sp^3)$ cross-coupling reactions. 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), NiCl₂.glyme (50 µmol), dtbpy ligand (75 µmol), K₂CO₃ (1.25 mmol), LiClO₄ (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 typ as ligand. In case of 13, an inseparable mixture of 13 and 13' was obtained, 41% purity.

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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 Ni¹ 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 on the reaction efficiency, as the para-, meta- and orthosubstituted 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-butyl 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 oxidation-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, the 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 that the Ni/tpy ligand combination is more compatible with electron deficient electrophiles to suppress homo-coupling.

In addition to examining the substituent positions and functional groups of the aryl halide substrates, we also investigated the tolerance of nucleophiles 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 4bromophenylethene, 3-bromofluorene, and 2-bromonaphthalene and also smoothly processed 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 groups including 6-bromoquinoline, heterocyclic 6protected bromoisoquinoline and Boc 6bromotetrahydroisoquinoline, 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 proved efficient carbon radial precursors in this cross-coupling reaction (26 to 31, 74% to 95% yield). Functional groups, including esters, methoxy group, trifluoromethyl group tolerated this Ni-catalyzed and 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).

In the CV screening studies (Figure 2B), β-bromostyrene also showed reactivity in the cathodic half-reaction and thus was briefly examined as an electrophile for the Heck-type like C(sp²)- $C(sp^3)$ 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 the dtbbpy ligand. According to entry 13, the tpy ligand exhibited the better selectivity by suppressing the homo-coupling product. Then the coupling reaction using βbromostyrene was optimized with the typ ligand. The improved yield and selectivity for the cross-coupling product $\mathbf{34}$ were obtained in the presence of the tpy ligand (83% yield, 90% selectivity) (Table S3, SI). As shown in Figure 3, both electronrich 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. anodic nucleophiles (3-bromopropiolate, However, other phenylacetic acid, potassium pivalate, and potassium phenyltrifluoroborate) didn't provide satisfactory results (see Figure S10 and the SI for more discussions).

To demonstrate potential applications of this Ni-catalyzed electrochemical C(sp²)–C(sp³) cross-coupling methodology, we first exploited the synthesis of pharmaceutical molecules containing the diphenylmethane structural component. Beclobrate analog (42, a hypolipidemic candidate^[50]) and (**43**, an antidepressant candidate^[51]) Bifemelane 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 drug candidates. Fenofibrate is a pharmaceutical molecule of the fibrate class and used to treat abnormal blood lipid levels.^[52] As shown in Figure 4C, Fenofibrate

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Figure 4. Applications of the Ni-catalyzed electrochemical C(sp2)–C(sp3) 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.

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 from a regular vial electrolyzer cell. Another new Clofibrate derivative lipid-lowering agent) was synthesized using (a 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). For practical applications of electrosynthesis, we believe flow cell electrolyzers are the appropriate reaction platform beyond vial cells. In fact, flow cells have been extensively used in organic redox flow batteries^[53] and have also received increasing attention in organic electrosynthesis.^[54, 55] To further demonstrate 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 (see part 6 Flow Cell Synthesis in the SI). It should be noted that 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(sp²)-C(sp³) cross-coupling reaction, a radicaltrapping experiment was conducted for the anodic half-reaction. As shown in Figure 5A, controlled potential electrolysis (at 1.2 V, Fc^{+/0}) of the potassium trifluoro(4-VS. (methoxycarbonyl)benzyl)borate and 2,2,6,6-tetramethyl-1piperidinyloxy (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 Cs₂CO₃ in the anodic oxidation process (Figure 5B and see the SI for detail). k^0 of potassium benzyltrifluoroborate and cesium phenylacetate were calculated as 5.56×10^{-5} cm/s and 1.39×10^{-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 crosscoupling reaction over phenylacetic acid / Cs₂CO₃ (30% yield). It is believed that the quick formation of the carbon radical is critical

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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, LiCIO₄ (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 NiCl₂-glyme + 25 mM dtbbpy (green), and 5 mM NiCl₂-glyme + 15 mM dtbbpy + 50 mM methyl 4-bromobenzoate (orange) in DMF with 0.2 M LiCIO₄ supporting electrolyte.

to trap the R-Ni^{II}-X intermediate, otherwise the R-Ni^{II}-X intermediate can promote the homo-coupling side reaction.

Electrochemical studies were conducted to gain additional mechanistic insights for the cathodic process. As shown in Figure 5C, 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 NiCl₂•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 corresponds to Ni^{II/I}, Ni^{I/0} redox couples, and the free ligand. When the methyl 4-bromobenzoate substrate was added, apparent increase of reductive current and disappearance of the return peak was observed for the Ni^{II/I} redox couples. This indicates that the Ni^I species, (dtbbpy)Ni^IBr (intermediate B in Figure 6B) is the reactive species for the oxidative addition of aryl halide and results in the formation of (dtbbpy)ArNi^{III}Br₂ (intermediate D in Figure 6B). The increased current intensity from 94 µA for the Ni^{II/I} redox couple to 134 µA in the presence of methyl 4-bromobenzoate is attributed the reduction of (dtbbpy)ArNi^{III}Br₂ to (dtbbpy)ArNi^{II}Br (intermediate E in Figure 6B). 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 S11). The potential of cathode was retained between -1.7 and -1.9 V (vs. Fc^{+/0}) during the reaction (Figure S12), and the observation further confirms that the Ni^{1/0} redox couple is not involved in the cathodic process.

To confirm the homogeneous reaction nature and stability of the Ni catalyst in the studied electrochemical C-C cross-coupling

reactions, a suit of control experiments was conducted. As shown in Figure 6A, after 50% conversion of a standard reaction between benzyl trifluoroborate and methyl 4-bromobenzoate, the electrodes and reaction mixture were separated (reaction 1 in Figure 6A). For the reaction mixture part, two fresh electrodes were added, and the resulting reaction mixture was electrolyzed at 3 mA current (reaction 2). The cross-coupling product, methyl 4-benzylbenzoate (1) was obtained in a yield of 94% after the bromide substrate was fully converted. The used electrodes were rinsed with dry DMF and then directly used as electrodes for a fresh reaction mixture in which no NiCl₂.glyme/dtbbpy catalyst was added (reaction 3 in Figure 6A). However, no cross-coupling product was observed in reaction 3 after electrolysis. We then further tested the catalytic capability of the Ni catalyst using the second batch of the substrate mixture which was added as solid into the reaction solution of reaction 2. For the second batch reaction (reaction 4 in Figure 6A), a yield of 92% was obtained, giving a total yield of 93% for methyl 4-benzylbenzoate (1). The CV curves which were collected after reaction 2 displayed the redox features as those of fresh NiCl₂.glyme/dtbbpy catalyst (Figure S13), indicating the good stability of the Ni catalyst. Classic Chugaev's reagent (dimethylglyoxime) tests were performed to confirm the quantitative retention of Ni2+ ions in the reaction solution after electrolysis in reaction 2 (Figure S14). However, there was no Ni detected in the used cathode in reaction 2. To further confirm there was no Ni deposition on the cathode electrode, a SEM study was conducted with the used carbon cathode in reactions 2 and 4, and no Ni element was detected (Figure S15). These control experiments collectively

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Figure 6. (A) Control experiments to confirm the homogeneous nature and stability of the NiCl_{2.}glyme/dtbbpy catalyst and (B) Proposed reaction mechanism for the Ni-catalyzed electrochemical $C(sp^2)$ – $C(sp^3)$ cross-coupling reaction.

confirmed that the homogeneous nature and stability of the Ni catalyst for the studied cross-coupling reactions, which is consistent with observed potential profile at -1.75 V of the cathode during electrolysis (Figure S12).

Based on the chemical and electrochemical studies, a 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^{III} 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^{II} catalyst **B**.

Compared to the reported photocatalytic cross coupling of benzoic trifluoroborates and aryl halides by Molander and coworkers,^[8] which relies on an iridium photocatalyst to activate trifluoroborates and regenerate a Ni⁰ catalyst, the key mechanistic difference of the present electrochemical coupling is that both the reactive carbon radical and Ni¹ intermediate are generated electrochemically. Without using the expensive iridium photocatalyst and the reactive Ni⁰ catalyst, the present electrochemical cross coupling is also capable of using alkyl trifluoroborate nucleophiles as radical precursors.^[56]

effective to handle reactive alkyl radicals under the investigated reaction conditions. Through optimization of reaction conditions and catalysts, it is promising to expand the scope of nucleophiles to alkyl and phenyl trifluoroborates, and even carboxylic acids for electrochemical cross couplings. It is also noted that after the public disclosure of this work as a pre-print version in ChemRxiv, ^[44] Hu et al. reported Ni catalyzed electrochemical cross-coupling reactions of toluene derivatives and aryl halides,[45] which is interesting and important for the challenging paired redox neutral electrosynthesis. We observed that reaction scope and efficiency of our work is better than those reported in Hu's work. In Hu's work, benzyl radicals were electrochemically generated through benzyl C-H activation. However, benzyl C-H activation is limited to electron rich toluene derivatives and is believed to limit the reaction scope and efficiency. In addition, we used a more affordable carbon anode than an FTO anode used in Hu's work.

Conclusion

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. 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 demonstrated in the flow-cell synthesis. 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 $C(sp^2)$ –

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C(sp³) 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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Conflict of interest: A patent application including the submitted results was filed.

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A redox neutral electrochemical $C(sp^2)-C(sp^3)$ cross-coupling paradigm is developed using bench stable substrates and Ni catalysts. The Ni-catalyzed electrochemical cross-coupling exhibits good reaction efficiency and practical applications and expands the synthetic toolbox to forge carbon-carbon bonds.

Jian Luo, Bo Hu, Wenda Wu, Maowei Hu, and T. Leo Liu* Page No. – Page No. Nickel Catalyzed Electrochemical C(sp²)–C(sp³) Cross-Coupling Reactions of Benzyl Trifluoroborate and Organic Halide