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Zinc-Free, Scalable Reductive Cross-Electrophile Coupling Driven by Electrochemistry in an Undivided Cell

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Abstract

Nickel-catalyzed reductive cross-electrophile coupling reactions are becoming increasingly important in organic synthesis, but application at scale is limited by three interconnected challenges: a reliance on amide solvents (complicated workup, regulated), the generation of stoichiometric Zn salts (complicated isolation, waste disposal issue), and mixing/activation challenges of zinc powder. We show here an electrochemical approach that addresses these three issues: the reaction works in acetonitrile with diisopropylethylamine as the terminal reductant in a simple undivided cell (graphite(+)/nickel foam(-)). The reaction utilizes a combination of two ligands, 4,4'-di-*tert*-butyl-2,2'-bipyridine and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine. Studies show that, alone, the bipyridine nickel catalyst predominantly forms protodehalogenated aryl and aryl dimer, whereas the terpyridine nickel catalyst predominantly forms biaryl and product. By combining these two unselective catalysts, a tunable, general system results because excess radical formed by the terpyridine catalyst can be converted to product by the bipyridine catalyst. As the aryl bromide becomes more electron rich, the optimal ratio shifts to have more of the bipyridine nickel catalyst. Lastly, examination of a variety of flow-cell configurations establishes that batch recirculation can achieve higher productivity (mmol product/time/electrode area) than single-pass, that high flow rates are essential to maximizing current, and that two flow cells in parallel can nearly halve the reaction time. The resulting reaction is demonstrated on gram scale and should be scalable to kilogram scale.

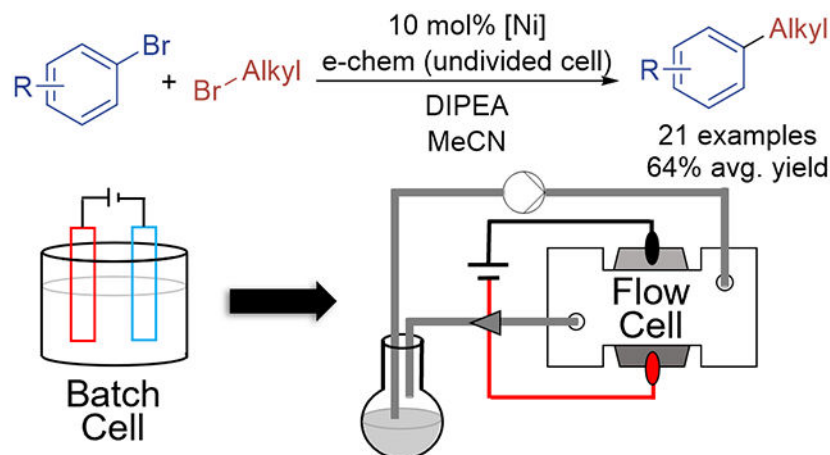
Graphical Abstract

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Supporting Information. Additional tables of data, electrochemical data, detailed experimental procedures, characterization data for isolated compounds, and copies of NMR data. This material is available free of charge via the Internet at <http://pubs.acs.org>.



Keywords

nickel; electrochemistry; cross-coupling; flow; cross-electrophile coupling; mechanism; multimetallic catalysis

The catalytic formation of C–C bonds is dominated by the coupling of pre-formed organometallic nucleophiles (e.g., organoboronic acids, organozinc reagents, silanes, Grignard reagents) with organic electrophiles.¹ Of the two coupling partners, organometallic nucleophiles are less abundant and are often synthesized from carbon electrophiles,² incurring additional synthetic steps. Methods based upon in situ organometallic reagent generation avoid additional steps,³ but all of these reactions are accompanied by stoichiometric metal salt generation. Cross-electrophile coupling generates the same products as cross-coupling, but directly from two electrophiles and without the need for stoichiometric metal, *in theory*.⁴ In practice, the use of metal reductants⁵ (e.g., Zn, Mn, Mg) or metal sacrificial anodes^{6,7,8} have been the most general strategies used for C(sp²)–C(sp³) bond formation (Scheme 1). Applications in industry and academia have almost exclusively generated stoichiometric metal waste (e.g., MnX₂, ZnX₂, or boron or silicon waste). Metal byproducts can be difficult to separate out, the disposal of which is highly regulated,⁹ and this has forced process changes in pharmaceutical applications.¹⁰ As cross-electrophile coupling matures, the realization of its green-chemistry potential on scale has become of increasing interest.

Besides stoichiometric metal waste, analyses at BMS,^{5b,8} Merck,¹¹ and Pfizer¹² have identified the major issues in scale-up to be heterogeneity/mixing, inconsistency of metallic reductant quality, the possibility of strong exotherms, and reliance on amide solvents (Scheme 1).¹³ While progress has been made, no approach has been able to make progress on all of these challenges without introducing new complexities. For example, mixing issues are avoided by packed-bed Zn columns,¹⁴ but still rely upon amide solvents and generate metal salts. Photoredox approaches avoid a heterogeneous reductant, but introduce co-catalysts and the need to shine light into the reactor.^{15,16,17} The organic reductant tetrakis(dimethylamino)ethylene (TDAE) avoids metal salts,¹⁸ but its amidinium salts are highly insoluble and TDAE is costly, air sensitive, and moisture sensitive.^{19,20}

Electrochemical approaches to reductive C–C bond formation were extensively studied in the 1970s and 1980s before seeing a recent renaissance,^{6,21} but most of these studies rely upon sacrificial metal anodes (generating stoichiometric metal waste) and/or amide solvents. Compared to soluble sacrificial reductants, sacrificial metal anodes avoid complications due to substrate or catalyst oxidation at the anode and the metal salts generated typically do not interfere with catalysis. However, because sacrificial anodes degrade over time, their use on scale or in flow can be more complicated.^{11,12} An MIT and Snapdragon team was the first to use a sacrificial amine terminal reductant for electrochemical C(sp²)-C(sp³) cross-electrophile coupling.²² We recently reported that amine terminal reductants could allow the use of acetonitrile instead of amide solvents,¹² which simplifies workup. However, both cases required the use of a divided cell with a Nafion™ cation exchange membrane which can be more complicated²³ to scale up due to chemical and mechanical stresses on the membrane.²⁴ In addition, divided cells typically have high cell resistance, sometimes requiring larger amounts of electrolyte,²⁵ complicating workup.²⁶ Li recently reported on a paired-electrolysis approach in NMP where the anodic oxidation of triphenylphosphine generates phosphonium bromide *in situ* which converts alcohols to alkyl bromides, the substrate for the cathodic cross-electrophile coupling reaction.²⁷ Rueping demonstrated the arylalkylation of alkynes using electrochemistry and photo-assisted electrochemistry to selectively form the *E* and *Z* isomers, respectively, using a terminal amine reductant in DMA.²⁸ These approaches use an undivided cell, but again rely on an amide solvent and high equivalents of coupling partners.

We show here the electrochemical cross-electrophile coupling of alkyl and aryl bromides using a common amine, diisopropylethyl amine (DIPEA),²⁹ as the terminal reductant / base in an undivided cell (graphite(+)/nickel foam(-)) with acetonitrile as the solvent and only 0.1 equiv of electrolyte. We demonstrate the affordable³⁰ scale up of this reaction in flow using two Micro Flow Cells by ElectroCell³¹ capable of producing 0.27 g of product per hour. Further scaling is possible with larger flow cells (up to 1 m²) from the same company, which should allow for scaling up to ~5 kg product/week.³²

Starting from conditions we reported previously for cross-electrophile coupling reactions in divided cells and inspired by some photoredox-driven cross-electrophile coupling reports, we found that by using DIPEA as the terminal reductant, the reaction is selective towards the product even in undivided cells. These reactions were run under constant current, using acetonitrile as the solvent, only 0.1 equiv (20 mM) tetrabutylammonium hexafluorophosphate (TBAPF₆) as the electrolyte,³³ and a combination of nickel bipyridine and nickel terpyridine catalysts.

As shown in Table 1, nickel, **L1/L2**, DIPEA, and electricity, are all necessary for product formation (entries 3–4,6–7). NiBr₂•3H₂O is lower cost than other nickel pre-catalysts, is available on large scale, and outperforms other pre-catalysts due to improved solubility (see Supporting Information Figure S1). Although this small amount of water is well tolerated (0.3 equiv H₂O from pre-catalyst), larger amounts of water (5% v/v) resulted in lower yield (entry 2). The reactions are also tolerant of air. While initial reactions were set up with exclusion of water and air, we later found that benchtop setup provided similarly good results (Supporting Information Figure S3). We found we could run reactions with nickel

stripped from the cathode by reversing the current for 0.2 F/mol before starting the reaction (entry 5), which could be an advantage in jurisdictions where nickel salts are regulated as carcinogens.³⁴ DIPEA was the optimal amine because it does not react with the alkyl halide. Triethyl amine provided lower yields due to *N*-alkylation (see Supporting Information S2). Several electrode materials were tested, and high yields were obtained with nickel foam as the cathode and graphite rod as the anode (entries 8–9). This is a practical advantage because they are easier to work with than RVC, which has a similarly high surface area, but is brittle.³⁵ The applied current was chosen to be 1.33 mA/cm². At higher current the selectivity decreased, forming more alkyl dimer and protodehalogenation of the aryl bromide (entry 10). However, lower current did not significantly improve the yield (entry 11). At lower temperatures, alkyl dimer formation increased (entry 12). LiBr can be used as an electrolyte instead of TBAPF₆, albeit with a decrease in yield from 89% to 66% (entry 13).

As we have reported in several studies,^{12,36} a two-catalyst multimetallic system was optimal.³⁷ We found that reactions of electron-poor aryl bromides with only terpyridine nickel catalysts provided reasonable yields of cross-product accompanied by bialkyl and unreacted aryl bromide (Scheme 2A, 2B). In reactions with a less reactive aryl bromide (4-tolyl bromide), the terpyridine-only system produced primarily bialkyl (Scheme 2C). In contrast, reactions with bipyridine nickel catalysts provided a low yield of cross-product along with protodehalogenated aryl (ArH) and aryl dimer with minimal consumption of alkyl bromide regardless of the identity of the aryl bromide (Scheme 2, see Supporting Information Figures S5-7 for full time course data with the different ligand ratios for three example substrate pairs). The addition of bipyridine nickel to reactions catalyzed by terpyridine nickel complexes decreases the amount of alkyl dimer formed and increases product yield. The optimal ratio appears to be dependent upon the relative reactivity of the aryl halide and the alkyl halide (Scheme 2). For very electron deficient aryl bromides, the terpyridine nickel catalyst on its own results in the best selectivity (Scheme 2A). However, for slightly electron deficient aryl bromides, a 3:1 ratio of terpyridine nickel catalyst to bipyridine nickel catalyst provided the best selectivity (Scheme 2B). As the aryl bromide becomes increasing electron-rich (and, therefore, less reactive for oxidative addition), the optimal ratio shifts to 1:1 ratio of the nickel catalysts (Scheme 2C). These findings contrast with cross-electrophile couplings of aryl bromides with alkyl bromides using metal reductants in amide solvents,³⁸ where reactions conducted with terpyridine ligands provide primarily alkyl dimer products and bipyridine ligands are optimal.

An open question with two-ligand nickel systems is the origin of the synergistic effect, as exemplified in Scheme 2C: how do two poor catalysts combine to result in high yields of cross-product? Based upon our own studies and literature data,^{39,40} we propose two connected catalytic cycles for product formation (Scheme 3). The first cycle is catalyzed by (**L1**)Ni and is poorly selective for product over bialkyl when the aryl bromide is deactivated for oxidative addition compared to the alkyl bromide. The mechanism of this cycle is likely related to the mechanism first proposed by Vannucci.⁴⁰ Based upon CV studies and analysis of the reaction cell potential, we propose that the accessible (**L1**)Ni^I intermediate⁴¹ reacts with both Ar-Br and Alkyl-Br, with a preference for Alkyl-Br, resulting in product formation

and a large amount of excess free Alkyl• that, on its own, would result in large amounts of Alkyl–Alkyl product.⁴² The second cycle is catalyzed by (**L2**)Ni and *relies upon excess Alkyl• from the (**L1**)Ni system for product formation*. The (**L2**)Ni⁰ catalyst, which should be accessible under these conditions,⁴¹ reacts almost exclusively with aryl bromide to form a relatively stable (**L2**)Ni^{II}(Ar)Br species that can capture excess Alkyl• generated by (**L1**)Ni to form cross-coupled product. While each catalyst is capable of product formation alone, they both suffer from poor selectivity. The combined catalysts complement each other, resulting in a synthetically useful system. This dual-catalyst system contrasts with a different system recently reported by Sevov, where a 2:1 ligand/nickel ratio was optimal, and their studies suggested ligand substitution was occurring during each turnover.^{7m,43}

The substrate scope for this simplified electrochemically-driven cross-electrophile coupling is similarly broad to reactions with metal reductants (Scheme 4). The two-catalyst system allows couplings with a broad array of substrates, such as couplings of aryl bromides with *ortho*-coordinating groups (**3i-j**)⁴⁴ and Lewis-basic nitrogen heterocycles (**3q-u**).⁴⁵ Primary and secondary alkyl bromides couple in good yield without the need for iodide additives.⁴⁶ Sterically hindered substrates such as neopentyl bromide or methyl 2-bromobenzoate resulted in lower yields. While our standard 3:1 **L1/L2** catalyst mixture was effective for a wide array of substrate pairs, it was especially useful for aryl bromides with electron-withdrawing groups. For aryl bromides that are slower to react by oxidative addition, such as 4-bromoanisole, yields could be improved by increasing the relative amount of **L2** ligand. In general, the selectivity of the reaction can be optimized by increasing the ratio of **L1** if there is unreacted alkyl bromide and/or high amounts of aryl H and aryl dimer, or by increasing the ratio of **L2** if there is unreacted aryl bromide and/or high amounts of alkyl dimer.

A key goal of this study was simplifying transition of the conditions to flow for scale up. Nickel-mediated electrochemistry has been reported in both single-pass (with slow flow) and in batch recirculation (with faster flow). The drastically different flow rates employed will impact mass transport and could result in different levels of productivity and selectivity. Further, both setups could be utilized with multiple cells in either parallel or series. We tested these configurations with our system and compared productivity (mmol product/time/electrode area).

Using the conditions we optimized in batch, we tested the two different flow setups (Scheme 5A). General reaction conditions for the flow optimization are shown in Scheme 5B. In most cases, we used 4,4',4''-trimethyl-2,2':6',2''-terpyridine (**L3**) and 4,4'-dimethyl-2,2'-bipyridine (**L4**) instead of **L1** and **L2**, respectively. These methyl ligands showed similar reactivity to the *tert*-butyl ligands, but can be synthesized in one step from picoline⁴⁷ or purchased at lower cost.⁴⁸ In the single pass setup,²² we screened residence time (average time that a given molecule is in the cell) and current density (Scheme 5C). We attribute ArH formation primarily to over-reduction of arylnickel(II) intermediates, as suggested by Sevov in their recent studies.⁷ⁱ Reduction of arylnickel(II) to form ArH is a complex function of current density, nickel concentration, turnover frequency, and mass transport. To avoid this side reaction in single-pass flow experiments, the catalyst loading was increased (from 5 to 10 mol%), and high selectivity toward the product could be regained (entries 1–3). However, further increasing the current density again resulted in diminished yield (entry 4).

In our experiments, batch recirculation is a superior approach to scale up electrochemical cross-electrophile coupling reactions in flow (Scheme 5D). In these reactions, each pass through the electrochemical cell is relatively fast and only a small amount of conversion is achieved per pass (Scheme 5A). While lower yields were obtained at low flow rate and nickel loading (Scheme 5D, entries 1 and 6), increasing nickel catalyst loading (entries 1–3) and increasing the rate of mass transport (by increasing the flow rate) improved selectivity and yield (entries 3–5 and 6–8). Increasing nickel concentration by decreasing the amount of solvent used was also effective, albeit limited by the solubility of reaction components (entries 9 and 10). Being able to tolerate higher current density allows recirculation to be more efficient (higher productivity per unit of electrode surface area) than batch or single pass flow (Scheme 5E). Multiple flow cells can be used to increase the electrode surface area and therefore decrease the total reaction time. Combining two flow cells in parallel resulted in slightly higher yield and efficiency than combining them in series (Scheme 5E). We hypothesize that better efficiency in batch recirculation is due to increased mass transport enabling the relatively slow cross-electrophile coupling reaction to primarily proceed outside of the electrochemical cell. The electrochemical cell is only needed to form nickel(0) at a pace sufficient to support the rest of the steps (Scheme 3). Using the optimized conditions for recirculation, we scaled up the reaction to gram-scale with two electrochemical cells in parallel. A smaller tubing size was used to avoid tubing rupture over longer periods of time, resulting in lower flow rates. At a lower flow rate with 11.4 mA/cm² current density, the yield decreased (as expected from our studies), but this slower flow could be compensated for by decreasing the current density. At 5.7 mA/cm² current density, we achieved 73% isolated yield (Scheme 5F). See SI for more details on how to set up the flow equipment and practical considerations.

In conclusion, we have developed a simple electrochemical approach for the scale up of C(sp²)-C(sp³) cross-electrophile coupling that avoids the use of metal reductants and amide solvents. By tuning the ligand ratio, a broader range of substrates can be coupled than with a single catalyst because the rate of alkyl radical generation can be adjusted to match the rest of the reaction steps. When translating this reaction to flow, increasing catalyst concentration and flow rate were instrumental in maintaining good yield at current densities practical for up to kg-scale synthesis. However, further scaling will require an improved understanding of the cathodic chemistry to allow for higher turnover frequency so that higher current densities can be supported.⁷¹ In addition, while the use of acetonitrile solvent and amine reductant is an improvement over amide solvents and zinc, in principle electrochemical approaches should allow for the use of still greener solvents and reductants. We are presently working on addressing these limitations and will report our results in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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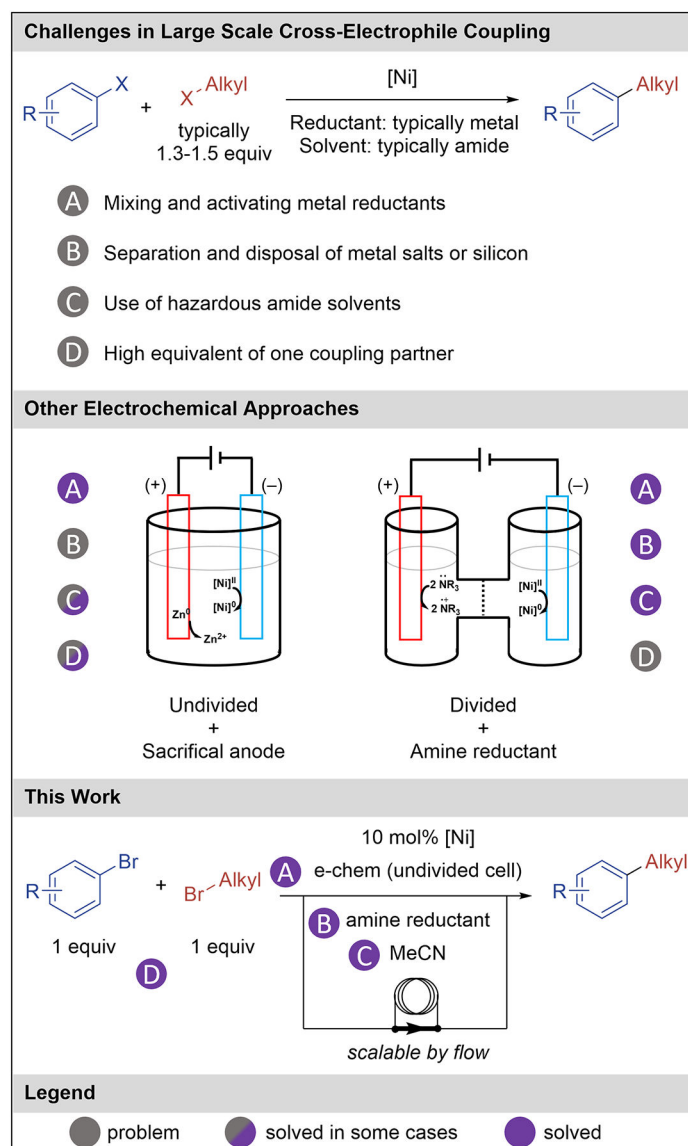
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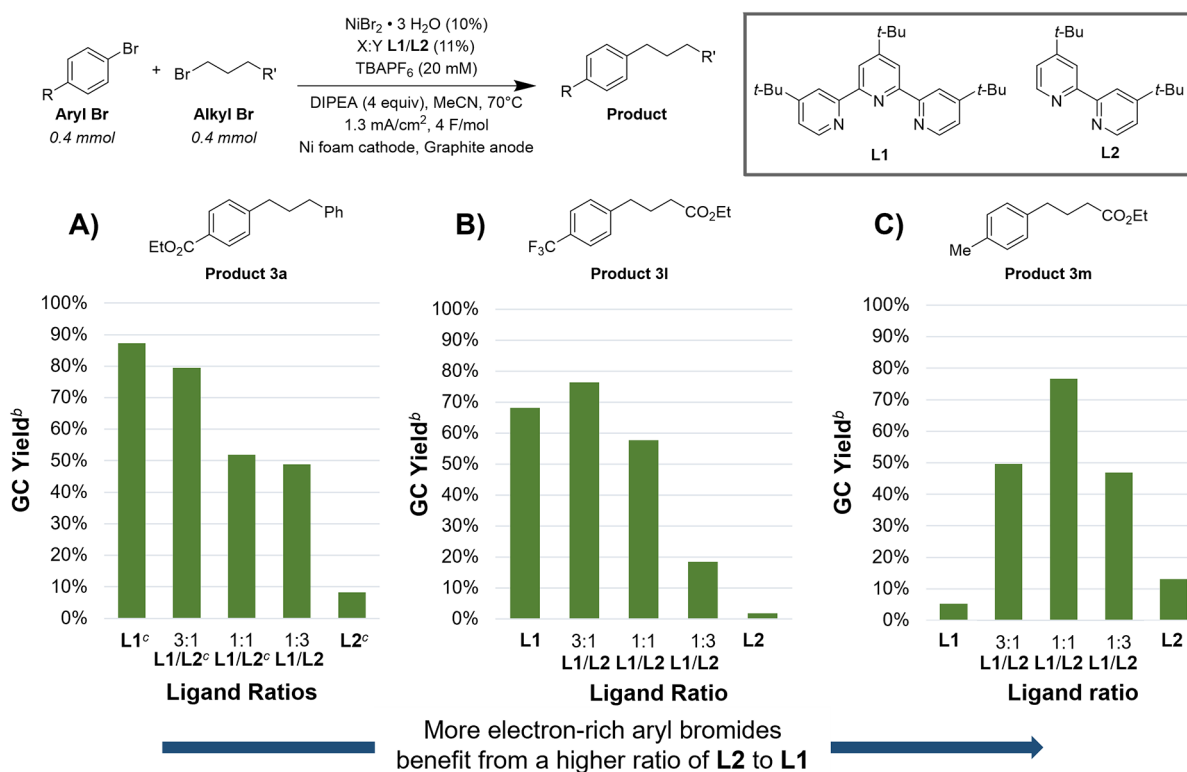
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29. For evidence that DIPEA is the terminal oxidant in these reactions, see Supporting Information page S35. Analysis of a large-scale reaction allowed isolation of *i*-Pr₂NH salts that would be derived from DIPEA oxidation followed by hydrolysis and protonation in workup.
30. The total cost of goods for our flow setup, including specialized pumps, two flow cells, electrodes, and power supplies, is \$6,254 without any special discounts. This is comparable to the cost of a single potentiostat for CV measurements. See Supporting Information Section 1.1 for details.
31. See Supporting Information Section 4.6 for large scale flow procedure.
32. Efficiency calculation for 1 m² electrode surface area scale-up using values from Scheme 5F:
- $$1 \text{ m}^2 \times \frac{10^4 \text{ cm}^2}{\text{m}^2} \times 5.71 \frac{\text{mA}}{\text{cm}^2} \times \frac{\text{A}}{10^3 \text{ mA}} \times \frac{\text{C}}{\text{A} \cdot \text{s}} \times \frac{6.24 \times 10^{18} \text{ e}^-}{\text{C}} \times \frac{\text{F}}{6.022 \times 10^{23} \text{ e}^-} \times \frac{\text{mol}}{4\text{F}} \times \frac{333.43 \text{ g}}{\text{mol}} \times \frac{\text{kg}}{10^3 \text{ g}} \\ \times \frac{3600 \text{ s}}{\text{h}} \times \frac{8 \text{ h}}{\text{day}} \times \frac{5 \text{ day}}{\text{week}} \times 73 \% \text{ yield} = 5.2 \frac{\text{kg}}{\text{week}}$$
33. Reactions with no added electrolyte started out with a high voltage due to the poor conductivity of the solution, but as the reaction progressed (and salts were formed) the voltage decreased, and final yields were similar to those with electrolyte added.
34. The use of nickel salts is increasingly regulated in Europe, for example (REACH). <https://echa.europa.eu/substance-information/-/substanceinfo/100.239.198> and <https://echa.europa.eu/substance-information/-/substanceinfo/100.202.593> and https://echa.europa.eu/documents/10162/13641/nickel_bg_annex1_en.pdf/12d24cbf-8f7e-0f1f-64c3-4992df4d00e8 (accessed on June 9, 2022).
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41. At this time, we cannot conclusively determine the oxidation state from which oxidative addition occurs from the two nickel complexes. CV studies on the individual complexes, the mixtures of complexes, and the cell potential of a constant-current reaction suggest (**L1**)Ni^IBr and (**L2**)Ni⁰ are the most accessible. See Supporting Information pages S14 to S25 and S36 to S39. Studies on oxidative addition with various ligands and electrophiles are in progress and will be reported in due course.
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43. While ligand exchange certainly is possible in this system (see Supporting Information pages S40–42), we do not currently think it plays an important role in this catalyst system because 1:1 [Ni]:[total L] is optimal, (**L1**)NiX₂ is competent for product formation on its own, and there is a continuous, predictable variation in yield and side-product formation with varying ratios of the two catalysts. In Sevov's study,^{7m} where ligand exchanged was determined to be operative, a 1:2 [Ni]:[total L] was optimal and leaving out either ligand resulted in ~5% product formation.
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47. We have found that 4-picoline (\$0.01/mmol) can be reliably converted into a mixture of 4,4'-dimethylbipyridine and 4,4',4''-trimethyl-2,2':6',2''-terpyridine that can be separated by sublimation. The corresponding reactions with 4-tert-butylpyridine (\$0.49/mmol) are not as reliable. Robo MT; Prinsell MR; Weix DJ 4,4',4''-Trimethyl-2,2':6',2''-Terpyridine by Oxidative Coupling of 4-Picoline. *J. Org. Chem* 2014, 79, 10624–10628. [PubMed: 25343728]
48. Currently, 4,4'-di-tert-butyl-2,2'-bipyridine (**L2**) is \$3.63/mmol, 4,4',4''-tri-tert-butyl-2,2':6',2''-terpyridine (**L1**) is \$65-84/mmol, and 4,4'-dimethylbipyridine (**L4**) is \$0.34/mmol. 4,4',4''-Trimethyl-2,2':6',2''-terpyridine (**L3**) is \$30/mmol (Strem), but we make both the bipyridine and the terpyridine in one step from picoline.⁴⁷ Data sources from REAXYS chemical source database. <https://www.reaxys.com/> (accessed on June 20, 2022).

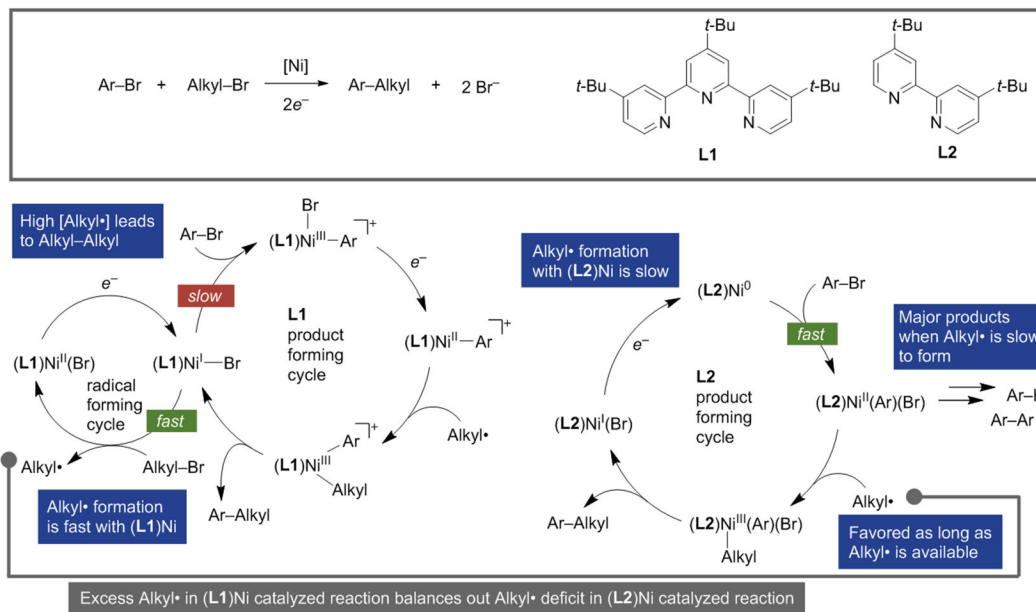


Scheme 1. Electrochemical Cross-Electrophile Coupling for Large Scale Applications.



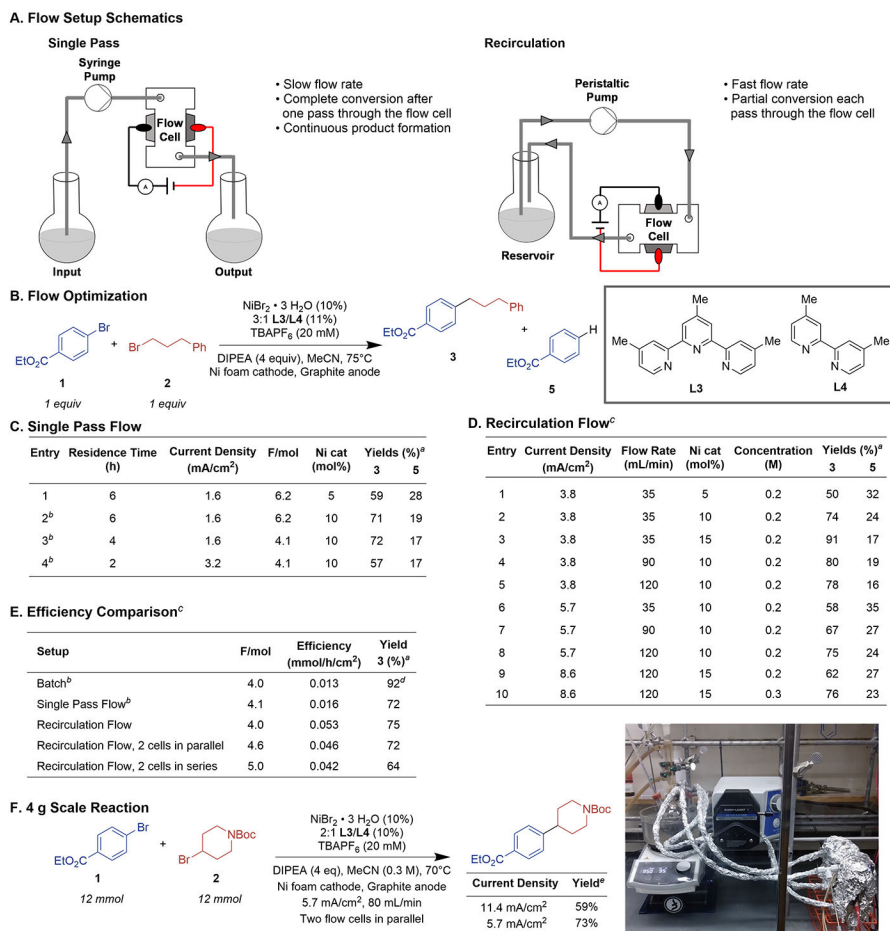
Scheme 2. Ligand Effects on Reaction Yield.^a

^aStandard Conditions: Aryl Br (0.4 mmol), Alkyl Br (0.4 mmol), $\text{NiBr}_2 \cdot 3 \text{H}_2\text{O}$ (0.04 mmol), Varying ratios of L1 / L2 (0.044 mmol), TBAPF_6 (0.04 mmol), DIPEA (1.6 mmol), MeCN (2 mL), 70 °C, 10 mA, Ni foam cathode (surface area = 7.5 cm²), graphite anode. ^bCorrected GC yield vs dodecane. ^cAverage of data from two reactions. A) Aryl Br = ethyl 4-bromobenzoate, Alkyl Br = 1-bromo-3-phenylpropane, B) Aryl Br = 4-bromobenzotrifluoride, Alkyl Br = ethyl 4-bromobutyrate, C) Aryl Br = 4-bromotoluene, Alkyl Br = ethyl 4-bromobutyrate



Scheme 3. Proposed Multimetallic Mechanism for Two-Catalyst Cross-Electrophile Coupling XEC.^a

^a Based upon CV data, we depict oxidative addition at (L1)Ni^IX and at (L2)Ni⁰. It is important to note that oxidative addition could occur from either oxidation state, but results in the same arylnickel(II) intermediate. Similarly, this proposal does not attempt to account for potential ligand exchange processes.



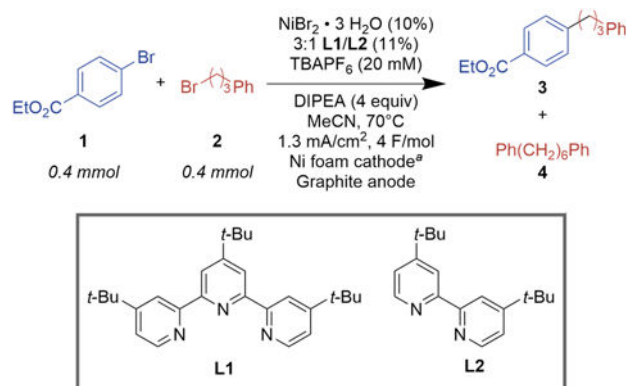
Scheme 5: Optimization of Electrochemical Cross-Electrophile Coupling in Flow.

^aCorrected GC yield vs 1,3,5-trimethoxybenzene. ^bLigands = 3:1 L1/L2. ^c4 F/mol,

^dCorrected GC yield vs dodecane. ^eIsolated yield.

Table 1.

Optimization of Electrochemical Cross-Electrophile Coupling in an Undivided Batch Cell.



Entry	Deviation from Standard Conditions	Yield (%) ^b			
		1	2	3	4
1	None	3	5	89	3
2	5% v/v H ₂ O	54	11	38	29
3	No L1 or L2	83	43	7	0
4	No $\text{NiBr}_2 \cdot 3 \text{H}_2\text{O}$	98	60	0	0
5	No $\text{NiBr}_2 \cdot 3 \text{H}_2\text{O}$, reverse current for 0.2 F/mol beforehand	1	8	69	5
6	No DIPEA	>99	68	0	0
7	0 F/mol ^c	99	93	0	0
8	RVC instead of Ni foam and graphite	45	17	41	18
9	Graphite instead of Ni foam	13	26	8	29
10	0.7 mA/cm ² instead of 1.3 mA/cm ²	0	2	80	11
11	2.0 mA/cm ² instead of 1.3 mA/cm ²	0	0	78	12
12	45 °C instead of 70 °C	35	16	35	31
13	LiBr instead of TBAPF_6	3	0	66	10

^aNi foam cathode surface area = 7.5 cm².^bCorrected GC yield vs dodecane.^cReaction mixture was stirred and heated for 4.3 h (length of reaction for 4 F/mol at 1.3 mA/cm²).