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Nickel-Catalyzed Electroreductive Coupling of Alkylpyridinium Salts and Aryl Halides

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Abstract

An electrochemical, nickel-catalyzed reductive coupling of alkylpyridinium salts and aryl halides is reported. High-throughput experimentation (HTE) was employed for rapid reaction optimization and evaluation of a broad scope of pharmaceutically relevant structurally diverse aryl halides, including complex drug-like substrates. In addition, the transformation is compatible with both primary and secondary alkylpyridinium salts with distinct conditions. Mechanistic insights were critical to enhance the efficiency of coupling using secondary alkylpyridinium salts. Systematic comparisons of the electrochemical and non-electrochemical methods revealed the complementary scope and efficiency of the two approaches.

Graphical Abstract

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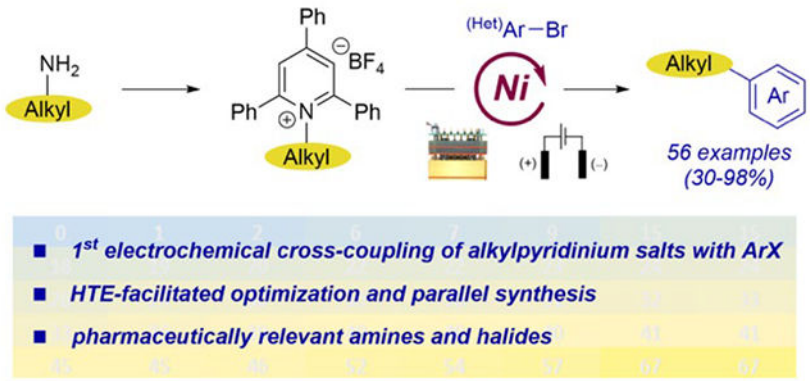
Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and data, additional optimization studies, CV studies, proposed catalytic cycle, NMR spectra (PDF)



Keywords

Nickel catalysis; electrochemistry; reductive cross-electrophile coupling; deamination; pharmaceutical discovery; high-throughput experimentation

INTRODUCTION

Organic electrochemistry is an emerging field that forgoes the use of chemical redox reagents, and instead relies on the electric potential at the electrode surface to drive redox processes.[1] This electrochemical approach is inherently more tunable than the use of chemical reductants, as the voltage can be matched to the potential of the catalysts. Electrochemistry also avoids difficulties in reproducibility often encountered with heterogeneous reductants, and can occur under neutral conditions in contrast to the use of basic homogeneous reductants, such as tetrakis(dimethylamino)ethylene (TDAE). However, the application of electrochemical conditions in reductive couplings remains nascent, particularly with regard to the alkyl electrophiles employed. Electroreductive $C(sp^2)–C(sp^3)$ couplings of aryl halides with alkyl halides and redox-active esters have been demonstrated (Scheme 1A),[2] and a recent report by Baran and co-workers on couplings using redox-active esters suggests that electrochemistry provides superior generality versus several non-electrochemical methods with pharmaceutically relevant building blocks.[3]

Given these advantages of electrochemical catalytic reactions, we sought to develop a nickel-catalyzed electroreductive coupling of alkylpyridinium salts with aryl bromides. Although electrochemical and electrophotochemical activation of alkylpyridinium salts has been demonstrated with various radical traps, such as Michael acceptors and heteroarenes,[4] electrochemically driven Ni-catalyzed couplings of Katritzky salts with aryl bromides have remained elusive.[5] A particular challenge in the development of electroreductive conditions for this nickel-catalyzed reaction is the relatively positive reduction potential[6] of alkylpyridinium salts ($E_{1/2}$ ~ −1.4 V vs. Fc/Fc^+) in comparison to the other alkyl electrophiles that have been used in electrochemical reductive couplings (alkyl halides and redox-active esters, Scheme 1A). Because alkylpyridinium salts are more easily reduced, they can be preferentially reduced instead of the Ni intermediates, leading to off-cycle byproduct formation via trapping of the dihydropyridyl radical, or dimerization or reduction of the alkyl radicals (Scheme 1B). In addition, the productive catalytic cycle relies on

balancing the relative rates of oxidation addition of the aryl halide and the activation of the alkylpyridinium salt. The difference in C–N cleavage rates of primary vs. secondary alkylpyridiniums often precludes their couplings under the same conditions, and the fast homolysis of secondary alkylpyridiniums may outcompete the oxidative addition of the aryl bromide. These challenges are exacerbated by the possibility for metallic electrodes to act as reductants even in the absence of current.

Despite these challenges, the potential utility of a deaminative electroredutive nickel-catalyzed cross-electrophile coupling motivated us to pursue this reaction. The construction of new $C(sp^2)–C(sp^3)$ bonds through transition metal-mediated cross-coupling reactions is a powerful tool to access pharmaceutical targets.[7] In particular, the direct coupling of two electrophiles represents an attractive strategy because it precludes the need to pre-form organometallic nucleophiles (R-M, in which M = [B], [Sn], [Zn], [MgX] *etc.*).[8] Alkylpyridinium salts are attractive substrates, because they are bench stable and conveniently prepared from the corresponding alkyl amines, which represent a class of ubiquitous building blocks that are frequently encountered in pharmaceutical research. Notably, an analysis of the internal inventory of Merck & Co., Inc., Rahway, NJ, USA revealed that >5000 primary and >4500 secondary alkyl fragments that are accessible in the form of amines (RNH_2) cannot be accessed from carboxylic acid, halide, or alcohol building blocks. We focused on aryl bromides as the coupling partners due to their high availability in comparison to more reactive aryl iodides. We herein disclose the first electroreductive couplings of alkylpyridinium salts with aryl bromides, leveraging the state-of-the-art high-throughput experimentation (HTE) for electrochemical development (Scheme 1C). This transformation is compatible with a broad scope of aryl and heteroaryl building blocks, as well as pharmaceutically relevant complex halides. Notably, the use of HTE technologies, including the recently disclosed 24-well high-throughput electrosynthesis reactor, HT*e*-Chem,[9] was critical in this study, as it enabled multi-parameter reaction optimizations and efficient evaluation of the substrate scope. The use of electrochemical mediators was also crucial to enable the efficient couplings of secondary alkylpyridinium salts.

RESULTS AND DISCUSSION

To commence our investigation, we selected mosapride-derived alkylpyridinium salt **1a** and 3-bromo-5-phenylpyridine **2a** as the model substrates. Both coupling partners possess UV chromophores and ionizable mass handles, allowing for facile analysis of reaction profiles by UPLC-MS analysis of the crude reaction mixtures (Scheme 2). The optimization study was initiated with $NiBr_2$(DME) as the catalyst, pyridine-2,6-bis(carboximidamide) dihydrochloride (**L1**) as the ligand, and NaI as the electrolyte at 60 °C. An evaluation of electrodes under constant current electrolysis using the HT*e*-Chem reactor at 35 μmol scale revealed that the combination of a cobalt sacrificial anode and stainless-steel cathode was most effective (Scheme 2A).[10] Reactions with more conventional cathodes, such as Zn and Mg, resulted in uncontrolled activation of the alkylpyridinium salt through background reduction directly at the metal. The optimal condition afforded the desired product **3a** in 65% assay yield (AY) as determined by UPLC-MS analysis of the crude reaction mixture. The use of tin and graphite cathodes was also effective with cobalt as

the anode, although the product was obtained with slightly lower or comparable yields (62% and 55% AY, respectively). In contrast, the use of other anode materials (Mg, Zn, and Al) was significantly less effective (<35% AY). Next, we evaluated catalyst/ligand combinations using a range of bi- and tridentate ligands against four nickel(II) salts (Scheme 2B). $NiBr_2$(DME) and $NiCl_2$(DME) were found to be the optimal nickel pre-catalysts, each affording the desired product **3a** in 60% AY. Control experiments confirmed that electricity was required for product generation. In an attempt to suppress side reactions (homo-coupling, radical addition into alkylpyridinium, *etc.*), a constant voltage electrolysis experiment was conducted and a cell potential of 0.9 V was found to be the optimal voltage (Scheme 2C) for both aryl bromides **2a** and **2b**. Unproductive pyridinium decomposition became dominant at higher voltages (1.0 – 1.1 V), while insufficient conversion was observed at 0.8 V. A similar reaction profile was observed under constant voltage or constant current electrolysis, whereby the remaining mass balance was accounted for by products formed via proto-dehalogenation, homo-coupling of the aryl bromide substrate and radical addition into alkylpyridinium.

With the optimal conditions using microscale HTE in hand, we next pursued preparative synthesis on an IKA ElectraSyn 2.0 at 0.3 mmol scale. As shown in Scheme 2D, product **3a** was obtained in 70% AY (entry 1). Increasing the temperature to 80 °C further improved the AY of **3a** to 88% (81% isolated yield, entry 2). Furthermore, constant current electrolysis (2.0 mA for 4 F/mol) also led to good product yield (78% AY, entry 3). While decreasing the reaction time to 6 h resulted in a lower yield (72%) (entry 4), it could be extended to 16 h (85%, entry 5). Use of NaI and tetrabutylammonium hexafluorophosphate ($TBAPF_6$) as electrolytes led to comparable yields of **3a** (81%, entry 6), suggesting that iodide anion is not necessary to promote these reactions via *in situ* formation of alkyl iodides. Negative control experiments showed that both nickel catalyst and ligand were required for good product yields (entries 8 – 9). Lastly, analogous to the results in Schemes 2A and 2B, electricity is required for product formation on 0.3 mmol scale (entry 10). Having the optimal conditions in hand, we investigated a two-step telescoped procedure involving sequential pyridinium formation and cross-coupling without isolation of the intermediate alkylpyridinium salt **1a**. As shown in entry 7, this telescoped procedure afforded the desired product in 58% isolated yield. Importantly, such telescoped methods are critical to effectively leverage the amine building blocks for library synthesis in the context of medicinal chemistry applications.

Having these preliminary results in hand, we next embarked on the elucidation of scope and generality of the electrochemical reductive cross-coupling by surveying the reaction of alkylpyridinium salt **1a** with diverse aryl- and heteroaryl bromides (Scheme 3). The evaluation of scope was conducted under HTE conditions at 35 μmol scale and the reaction efficiency was assessed using Liquid Chromatography Area Percent (LCAP) of the desired product obtained from the UPLC-MS traces of the crude reaction mixtures at 210 nm. As summarized in Scheme 3, the reaction displayed excellent functional group tolerance with pharmaceutically relevant scaffolds. Heteroaryl bromides, such as naphthyridine (**Br-15**), imidazopyrazine (**Br-16**), oxadiazole (**Br-25**), benzoxazole (**Br-32**), pyrrole (**Br-34**), pyridine (**Br-24**, **Br-36**), and triazole (**Br-38**) were suitable substrates

and afforded the desired cross-coupled products with moderate to good LCAPs (24 to 57% LCAP). Functional groups such as unprotected alcohols (**Br-33** and **Br-37**), phenols (**Br-13**), amides (**Br-18**), Boc-protected (**Br-11**, **Br-21**, and **Br-30**) or free amines (**Br-31**), nitriles (**Br-23**), ketones (**Br-20**), free carboxylic acids (**Br-28**) and aldehydes (**Br-40**) were tolerated under the reaction conditions. Notably, boronic ester (**Br-22**) was also compatible, providing possibilities for further product derivatizations via cross-coupling. In addition, we note that although product LCAP data does not translate directly to isolated yields, the scalability of this electroreductive method was demonstrated by performing select reactions at 0.3 mmol scale using IKA ElectraSyn,[11] and the isolated yields ranged from 30% to 88%. For substrates with >20% product LCAP, good to excellent isolated product yields were generally observed.

To compare the scope and limitations against non-electrochemical conditions,[8d] the set of aryl bromide substrates shown in Scheme 3 were also evaluated using previously reported non-electrochemical methods with Mn^0 powder or tetrakis(dimethylamino)ethylene (TDAE) as reductants. As illustrated in Scheme 4, use of Mn^0 as the reductant led to lower product LCAPs than obtained using electrochemistry for most substrates. This comparison indicates that electrochemistry can serve as a reliable alternative to Mn powder as the reductant for the cross-coupling reaction.[12] TDAE, on the other hand, provided comparable or higher LCAPs to electrochemistry for approximately half of the substrate set. Unlike metal powders, homogeneous reductants such as TDAE can be dosed in a more consistent manner for microscale HTE and hence are more suitable for applications in automated or nano-scale chemical synthesis. However, TDAE gave lower product LCAPs for reactions with substrates bearing certain functional groups, such as unprotected amine (**Br-31**), aliphatic alcohol (**Br-33** and **Br-37**) and carboxylic acid (**Br-28**) consistent with previous reports.[8d] In these cases, electrochemistry and Mn^0 proved to be more effective. Taken together, these results demonstrate that the systematic elucidation of the scope and limitations of electrochemical and non-electrochemical protocols is important to best leverage these processes for accessing the broadest chemical space.

The encouraging scope with aryl bromides in Scheme 3 prompted us to investigate the newly developed reductive cross-coupling reaction using “Informer” halides, which are a standardized set of 18 medium to complex, drug-like aryl halides. This halide set was introduced in 2016 to assess the applicability of cross-coupling reactions for the late-stage functionalization of pharmaceutical targets.[13] As shown in Scheme 5, 9 out of 18 substrates in the informer halide set (**X1**, **X2**, **X4**, **X5**, **X6**, **X8**, **X12**, **X14**, and **X15**) afforded the desired product with >20% LCAP for the couplings with alkylpyridinium salt **1a**. Importantly, this hit rate is comparable with that reported for the more well developed Pd-catalyzed Buchwald–Hartwig C–N couplings.[14] Proto-dehalogenation and unconverted starting materials accounted for the majority of the mass balance for unsuccessful reactions (**X3**, **X7**, **X9**, **X10**, and **X11**). In addition, while aryl iodides (**X14** and **X15**) generated the desired products in moderate yields, aryl chlorides (**X16 – X18**) were ineffective substrates for this transformation.

Next, we subjected a diverse set of alkylpyridinium salts derived from simple and biologically relevant primary amines to the reductive cross-coupling reaction using

3-bromoanisole as the aryl halide. As shown in Scheme 6, a number of primary alkylpyridinium salts were compatible with this transformation, furnishing the desired products in good to excellent isolated yields at 0.3 mmol scale. Functional groups such as Weinreb amides (**3c**), esters (**3g**, **3m**, **3o** and **3q**), alcohols (**3e**), phenols (**3r**), ketals (**3g**), acetals (**3h**), sulfonamides (**3k**), and azetidines (**3f**) were well tolerated and generated the corresponding products in good yields (53 – 88%). Substrates with an electron-rich heteroaromatic ring (**3d**) furnished the products in a slightly diminished yield (34%). The utility of this methodology to functionalize drug-like targets is highlighted by the utilization of alkylpyridinium salts derived from amine-based natural products, pharmaceuticals and pharmaceutical intermediates, or amino acids (**3g**, **3n**, **3o**, and **3q** – **3v**). Notably, amino acids such as lysine, 2,4-diaminobutyric acid (DAB), and 2,3-diaminopropionic acid (DAP) (**3t** – **3v**) successfully underwent cross-couplings to generate the desired products in excellent yields, paralleling the efficiency of our previously published non-electrochemical deaminative arylation of amino acids.[8d]

Despite the breadth of possible couplings with primary alkylpyridinium substrates, couplings of secondary alkyl pyridiniums and aryl bromides such as those illustrated in Scheme 7a formed only trace quantities of product under the developed conditions. We hypothesized that these lower yields might stem from a mismatch in the rates of oxidative addition of the aryl halide versus radical generation from the alkylpyridinium salt. Such coupling inefficiencies resulting from mismatched rates of activation are common in conventional cross-electrophile coupling reactions.[2f] This hypothesis was supported by measurable product formation, albeit in modest yields (35% – 66%), from reactions of secondary alkylpyridinium salts and activated aryl bromides (**3z**) or aryl iodides (see SI).

We sought to further improve couplings of secondary alkylpyridinium salts through a catalyst-controlled, rather than substrate-controlled, strategy to broaden the scope of the reaction. Our approach involved evaluating nickel-ligand complexes that could more rapidly activate aryl bromides than complexes of **L1**. More reactive catalysts could also allow for coupling reactions to be performed at mild temperatures. This factor is particularly important because secondary alkyl pyridinium salts rapidly fragment upon reduction at the standard conditions of 80 °C, as evidenced by irreversible voltammograms even when scanned at high rates of 1500 mV/s (see SI). It is only at room temperature that the reduction of secondary alkyl pyridinium salts is reversible, while CVs of primary alkyl pyridinium salts are reversible even at elevated temperatures (See SI). However, reactions catalyzed by Ni(**L1**) complexes at room temperature provide low conversion of the aryl bromide (<30%, see SI).

We targeted catalyst systems with complexes of very electron-rich ligands (**BPI**) or bidentate ligands (**tbbpy**, **PyOx**). Previous work from the Sevov group has shown that electrochemical cross-electrophile coupling with such complexes alone is low-yielding, but yields can be dramatically improved when a redox-matched mediator is added to reaction mixtures.[2e–g] The three ligand-mediator combinations **A-C** that were previously found to be effective for couplings of secondary alkyl bromides were evaluated for alkylpyridinium couplings (Scheme 7A). Reactions with combination **A** generated very low yields of product with or without the mediator. We attributed this result to the very negative reduction potential

of the catalyst system (−1.71 V vs Fc/Fc^+), which allows for preferential reduction of the alkylpyridinium at milder potentials (−1.43 V). Reactions performed with catalyst combinations that are reduced at increasingly mild potentials formed product in increasingly high yields at 80 °C (58% for combination **B**, 72% for combination **C**). Lowering the temperature of reactions catalyzed by combination **B** further increased product yields to 96%. Finally, the mediators were found to be critical to achieving high product yields.

The optimized conditions for reactions of secondary alkylpyridinium salts are detailed in Scheme 7B. Reactions were performed at a constant current of 2 mA up to a cell voltage of 1.4 V, at which point the system maintained a cell voltage of 1.4 V until the 2.5 F/mol capacity was reached. This simple program mitigates catalyst decomposition from high cell potentials that can exceed 2.5 V near the end of the electrolysis period. Reactions can also be performed at a constant voltage of 1.4 V to form products in only 5–10% lower yields than the voltage-capped procedure (see SI). A wide range of aryl and heteroaryl bromides undergo coupling under these conditions with both cyclic and acylic alkylpyridinium salts. Reactions are high yielding with electron-deficient aryl bromides. Gratifyingly, reactions of electron-rich aryl bromides that are classically challenging for reductive couplings[3] also form the desired products in good yield (**3af**, **3ag** and **3ai**).

Collectively, the distinct conditions for couplings of secondary alkyl pyridinium salts provide a better match between the rates of activation for aryl versus alkyl electrophiles over the conditions under which primary alkyl pyridinium salts are coupled. In particular, the reactive Ni(**tbbpy**) complex serves to accelerate activation of the aryl bromide compared to Ni(**L1**), while the decreased reaction temperature slows the fragmentation of the reduced 2° alkyl substrate. In contrast, couplings of primary alkyl pyridinium salts require elevated temperatures for alkyl radical formation from primary alkyl substrates and can be paired with Ni-ligand complexes that have attenuated reactivity towards aryl halides. It is likely because of this balance between activation rates that the catalyst systems for primary and secondary couplings are not interchangeable (see SI). These results emphasize the importance of having libraries of catalyst systems with complementary reactivity to achieve the broad substrate scope for medicinal chemistry applications.

Finally, we conducted a multi-dimensional library synthesis of 48 distinct products via the reductive cross-coupling of 6 aryl bromides against 4 primary and 4 secondary alkylpyridinium salts using HT*e*-Chem (Scheme 8). The aryl bromides were chosen from Scheme 3 with a range of functional groups. Notably, we focused specifically on alkylpyridinium salts derived from amines bearing alkyl fragments that were inaccessible from other building blocks that are commonly used for reductive couplings, namely, carboxylic acids, alcohols and alkyl halides. As shown in Scheme 8, moderate to high product LCAP's were observed for most substrate combinations with primary and secondary alkylpyridinium salts (see SI for telescoped reaction results). Consistent with the results in Schemes 3, 6 and 7, both electron-deficient and challenging electron-rich aryl halides (e.g., **Br-35**) afford the product in good product LCAP's. Thus, these transformations hold promise to rapidly expand the diversity of primary and secondary alkyl-substituted aromatic compounds of high relevance to medicinal chemistry.

CONCLUSION

In summary, this manuscript details the first general electrochemical transformation for the reductive coupling of alkylpyridinium salts with aryl bromides and iodides. Leveraging the recently developed 24-well HTE electrochemical reactor, HT*e*-Chem, rapid parallel reaction optimization, evaluation of a large set of substrates and multi-dimensional library synthesis were achieved. To the best of our knowledge, the use of Co sacrificial anodes (versus Mg and Zn) to minimize thermal reactivity has not been demonstrated in similar reductive cross-electrophile couplings under electrochemical conditions. The reaction was found to be effective with various pharmaceutically relevant functionalities and drug-like "informer" halides. The generality of this methodology now adds alkyl amines to the growing list of reliable coupling partners for electrochemical reductive couplings with a reaction scope that paralleled or surpassed that of well-established electrophiles, such as redox-active esters or alkyl halides.[3] Notably, the reaction efficiency was generally higher than non-electrochemical couplings using Mn^0 powder as the terminal reductant across a range of substrates. In addition, electrochemistry provided a complementary reaction scope to conditions employing TDAE. In addition, careful mechanistic considerations to match the relative rates of radical formation with oxidative addition to the aryl halide were imperative to achieve reaction generality with both primary and secondary alkylpyridinium substrates. While the primary alkylpyridinium salts demonstrated a broad scope at elevated reaction temperature, secondary alkylpyridinium salts required a distinct reaction condition that featured the use of a redox-matched mediator and lower reaction temperature to provide a better match between the aryl and alkyl coupling partners. Excitingly, the possibility of conducting library synthesis using microscale HTE further highlighted the synthetic relevance of this transformation in the context of medicinal chemistry to generate a large array of cross-coupled products in a material-sparing manner. Taken together, this study highlights the power of HTE technologies for enabling new pharmaceutically relevant electrochemical transformations that provide complementary efficiency or chemical space access to their non-electrochemical counterparts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(10). We also evaluated the impact of Co co-catalysis with a few different anode materials and Co salts, and observed no signficant impact on the reaction outcome. See SI for details.

(11). Although the reaction was optimized in constant voltage mode in Scheme 2, we occasionally experienced difficulty running the reactions to full completion. In these cases, constant current mode (2 mA, 4 F) was used and no significant compromise in reaction efficiency was observed. We also demonstrated in Scheme 2D that the reaction can be run either in constant voltage or constant current mode.

(12). In addition to Mn^0, we also attempted to use Zn^0 to evaluate the aryl halide scope. However, dosing Zn^0 into the 96-well plate was challenging and the results may not be reproducible[000].

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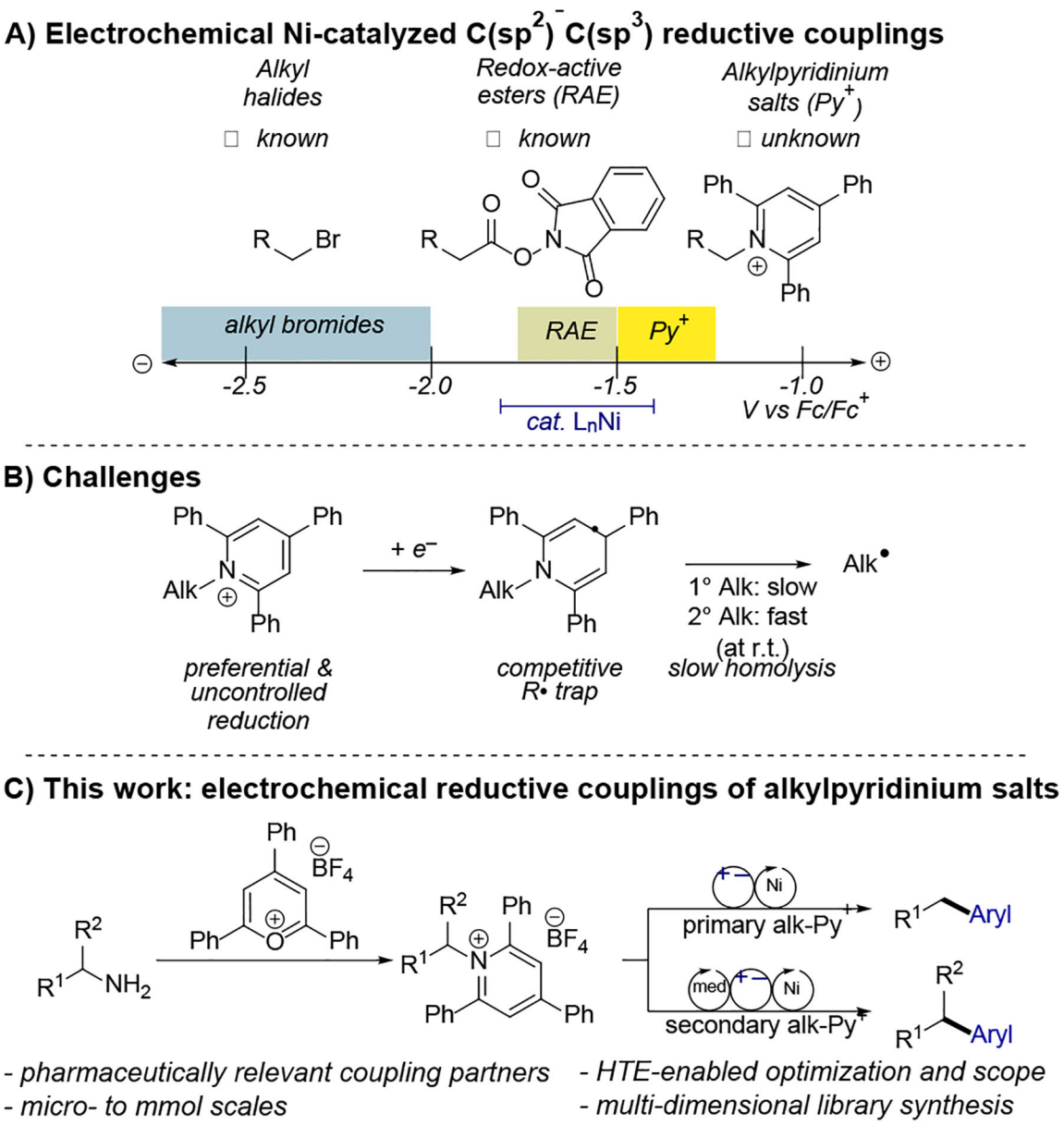
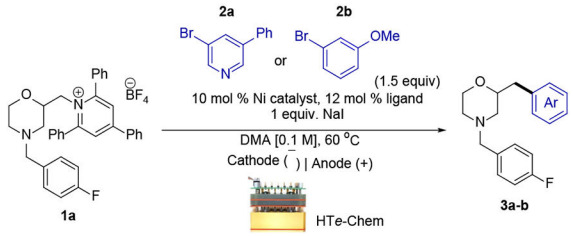


Scheme 1.
Electrochemical, Ni-catalyzed cross-electrophile couplings



(A) Cathode/anode screen (using ArBr 2a)

Cathode/Anode	Graphite (–)		Tin (–)		Stainless Steel (–)	
	w/ e-	w/o e-	w/ e-	w/o e-	w/ e-	w/o e-
Mg (+)	15	31	24	31	14	19
Zn (+)	27	31	32	45	30	39
Al (+)	5	0	8	0	5	0
Co (+)	55	0	62	0	65	0

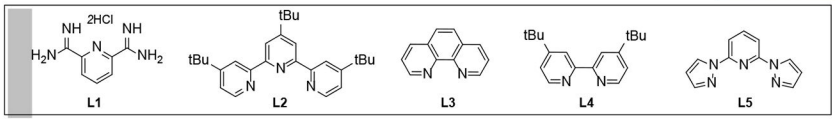
(B) Catalyst/ligand screen (using ArBr 2a)

Catalyst/Ligand	w/ e-					w/o e-
	L1	L2	L3	L4	L5	L1
$NiBr_2(DME)$	60	40	6	19	10	0
$NiCl_2(DME)$	60	43	6	17	11	0
$Ni(OAc)_2•4H_2O$	31	36	7	12	9	0
$Ni(acac)_2$	29	23	7	19	13	0

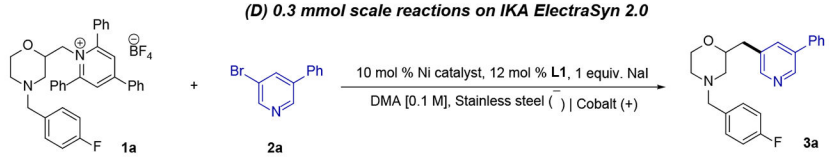
(C) Constant voltage screen (using ArBr 2a and 2b)

Cathode/voltage	Graphite (–)		Tin (–)		Stainless Steel (–)	
0.8 V	29	54	36	31	35	55
0.9 V	56	48	59	65	62	70
1.0 V	40	45	46	55	49	47
1.1 V	25	46	38	46	32	52
ArBr	**2a**	**2b**	**2a**	**2b**	**2a**	**2b**

Lowest Yield — Highest Yield



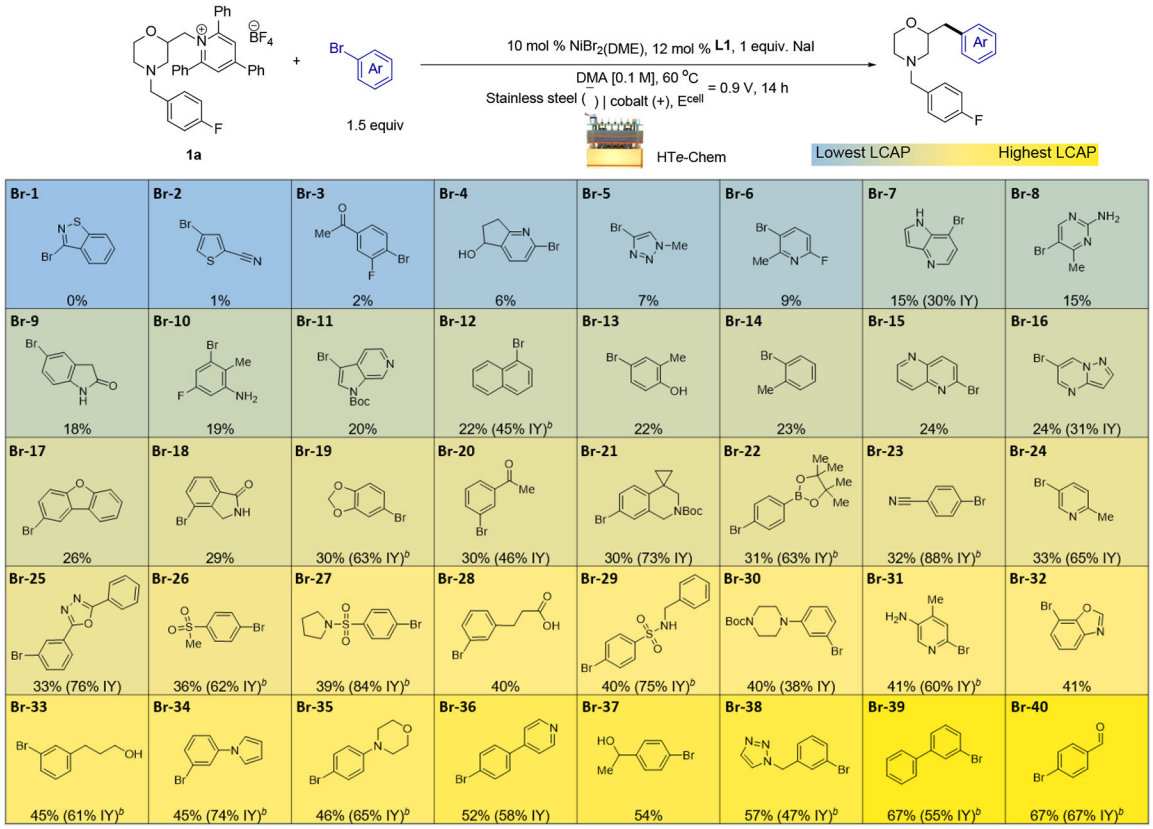
(D) 0.3 mmol scale reactions on IKA ElectraSyn 2.0



Entry	Temperature (°C)	Voltage/time	Yield (%)[b]
1	60	0.9 V / 10 h	70
2	80	0.9 V / 10 h	88 (81[c])
Deviations from standard condition (entry 2)			
3	2.0 mA for 4 F/mol instead of constant voltage		78
4	6 h electrolysis time instead of 10 h		72
5	16 h electrolysis time instead of 10 h		85
6	$TBAPF_6$ (1 equiv) as electrolyte instead of NaI		81
7	telescoped pyridinium synthesis and cross coupling		58[c]
8	no nickel catalyst		16
9	no ligand		14
10	no electricity		0

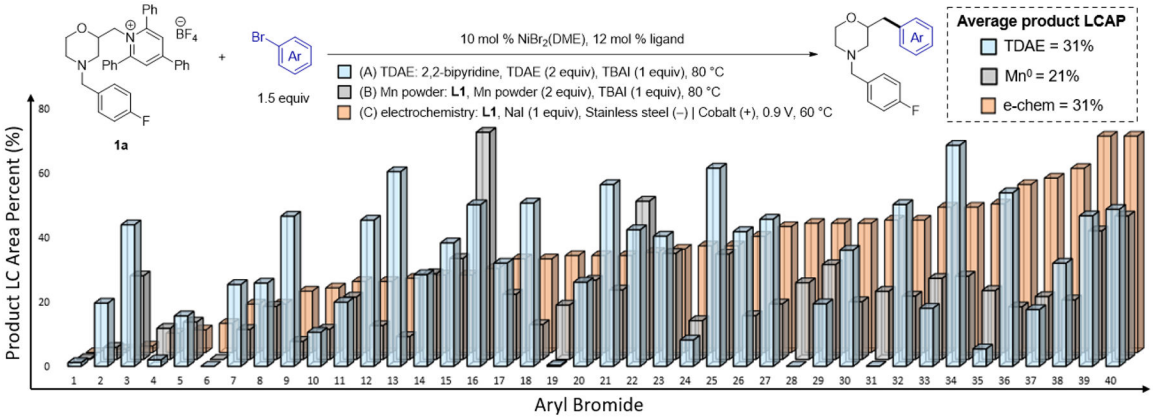
Scheme 2. Reaction optimization[a]

[a]Reactions were performed at 35 μmol scale for HTE experiments (1.0 mA or constant voltage) and at 0.3 mmol scale for IKA ElectraSyn experiments. Numbers in each box in the heat maps represent product assay yields determined by UPLC-MS of the crude reaction mixtures using 4,4'-di-tert-butylbiphenyl as the internal standard. Voltage refers to the applied cell voltage between the cathode and the anode. Conditional formatting was applied to indicate the range of product yields (see the key above). [b]Assay yields as determined by UPLC-MS using 4,4'-di-tert-butylbiphenyl as the internal standard, unless otherwise indicated. [c]Isolated yields following silica gel chromatography.



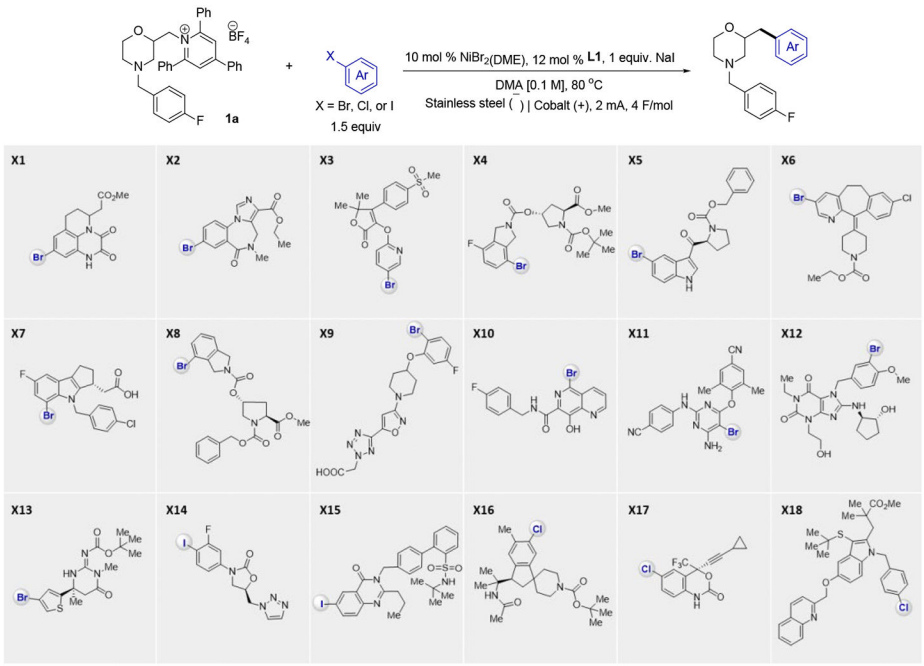
Scheme 3. Scope of ArBr[a]

[a]Numbers outside the parenthesis indicate the product LCAP's at 35 μmol scale. Formation of triphenylpyridine was not considered for LCAP determinations. Numbers inside the parenthesis indicate isolated yields (IY) at 0.3 mmol scale. Conditional formatting was applied to indicate the range of LCAPs. Microscale condition: alkylpyridinium salt (35 μmol, 1 equiv), ArBr (52.5 μmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), L1 (12 mol %), NaI (1 equiv), DMA (0.1 M), cobalt (+), stainless steel (–), 0.9 V, 60 °C, 14 h. 0.3-mmol scale condition: alkylpyridinium salt (0.3 mmol), ArBr (0.45 mmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), ligand (12 mol %), NaI (1 equiv), DMA (0.1 M), cobalt (+), stainless steel (–), cell potential 0.9 V, 80 °C, 14 h. [b]Constant current mode was used (2 mA, 4 F/mol).



Scheme 4. Dependence of ArBr scope on reaction conditions[a]

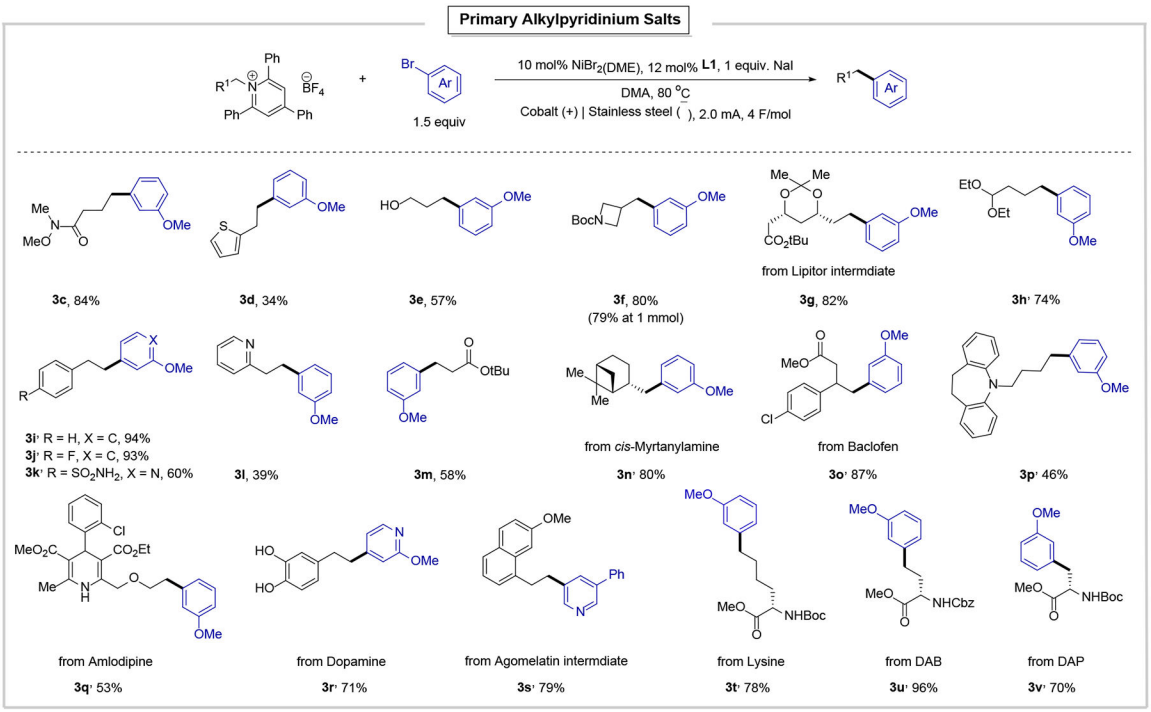
[a]LCAP data for reactions performed under three different conditions. Formation of triphenylpyridine was not considered for LCAP determinations. Conditions: (A) TDAE: alkylpyridinium salt (10 μmol, 1 equiv), ArBr (15 μmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), 2,2-bipyridine (12 mol %), TDAE (2 equiv), TBAI (1 equiv), DMA (0.1 M), 80 °C, 24 h (B) Mn powder: alkylpyridinium salt (10 μmol, 1 equiv), ArBr (15 μmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), **L1** (12 mol %), Mn^0 (2 equiv), TBAI (1 equiv), DMA (0.1 M), 80 °C, 24 h. (C) Electrochemistry: alkylpyridinium salt (35 μmol, 1 equiv), ArBr (52.5 μmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), **L1** (12 mol %), NaI (1 equiv), DMA (0.1 M), cobalt (+), stainless steel (–), cell potential 0.9 V, 60 °C, 14 h.



Informer Halides	Ar-Br													Ar-I		Ar-Cl		
	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12	X13	X14	X15	X16	X17	X18
LCAP (%)	79	28	0	23	45	43	0	34	0	0	0	31	14	72	27	0	0	0
Yield (%)	47[b]	21[c]	-	32[c]	55[b]	45[c]	-	43[c]	-	-	-	31[c]	33[c]	38[b]	26[b]	-	-	-

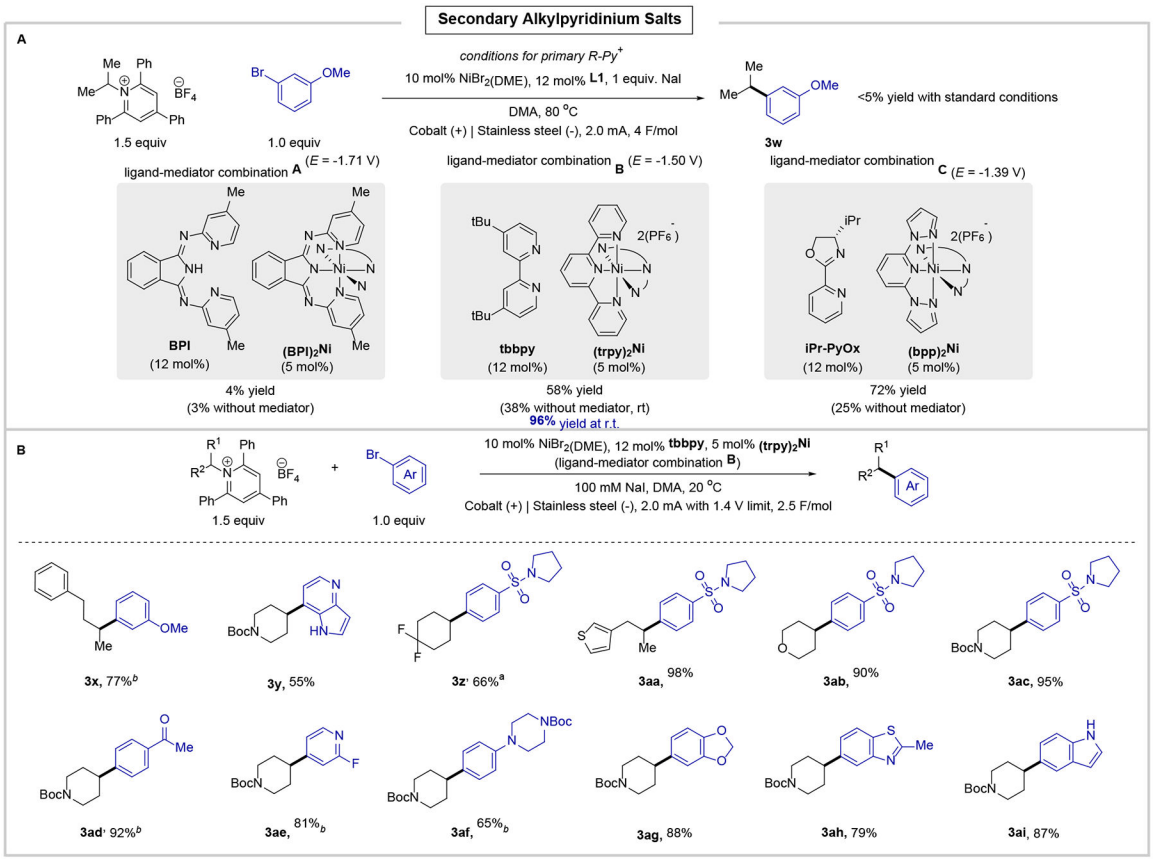
Scheme 5. Scope of "informer" halides[a]

[a]LCAP data for reductive couplings of alkylpyridinium salt **1a** and informer halides at 0.3 mmol scale. Formation of triphenylpyridine was not considered for LCAP determinations. Conditional formatting gradient is similar to Scheme 3. Reactions were performed at 0.3 mmol scale on IKA ElectraSyn 2.0. Conditions: alkylpyridinium salt (0.3 mmol, 1 equiv), halide (0.45 mmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), **L1** (12 mol %), NaI (1 equiv), DMA (0.1 M), cobalt (+), stainless steel (–), 2 mA, 4 F/mol, 80 °C. [b]Isolated yields following silica gel chromatography. [c]NMR yields using 1,3,5-trimethoxybenzene as the internal standard.



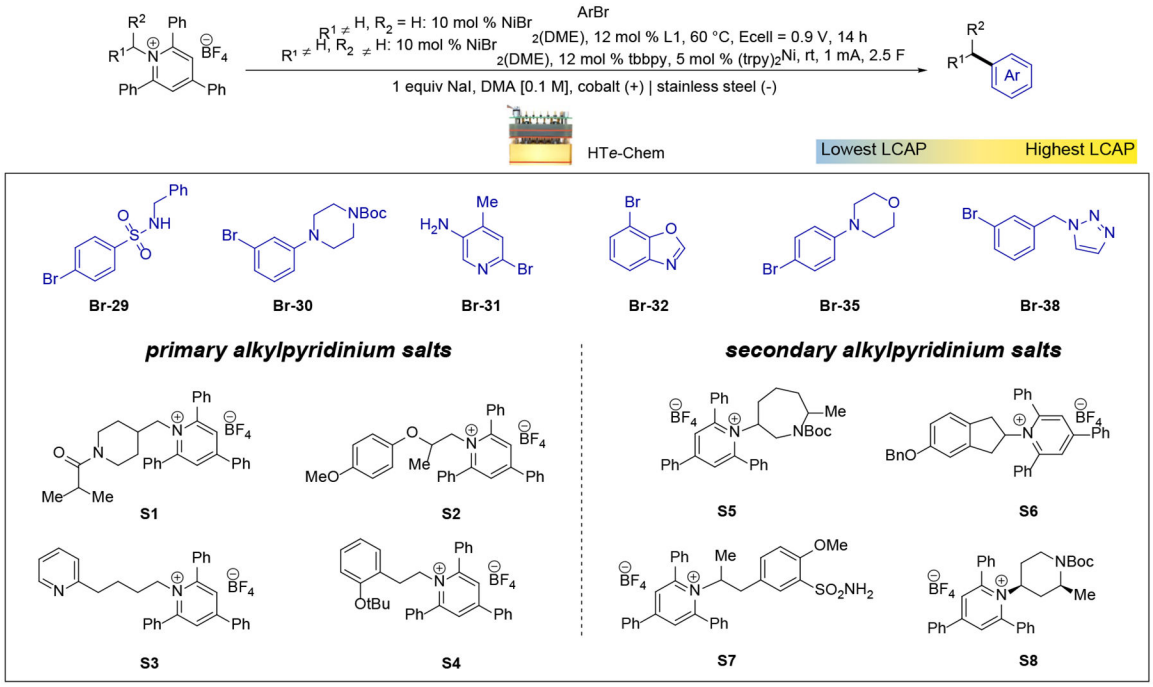
Scheme 6. Scope of primary alkylpyridinium salts[a]

[a]Reactions were performed at 0.3 mmol scale on IKA ElectraSyn 2.0. Yields refer to isolated yields following silica gel chromatography unless otherwise indicated. Conditions: alkylpyridinium salt (0.3 mmol, 1 equiv), aryl bromide (0.45 mmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), **L1** (12 mol %), NaI (1 equiv), DMA (0.1 M), cobalt (+), stainless steel (–), 2 mA, 4 F/mol, 80 °C.



Scheme 7. Optimization and scope of secondary alkylpyridinium salts

(a) Development of electroreductive coupling of 2° alkyl pyridiniums and aryl bromides; (b) Substrate scope with 2° alkyl pyridiniums. Reported yields are isolated yields. Conditions: aryl halide (0.30 mmol, 1 equiv), alkylpyridinium salt (0.45 mmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), tbbpy (12 mol %), $[Ni(trpy)_2][PF_6]_2$ (5 mol %), NaI (100 mM), DMA (3 mL), cobalt anode, stainless steel cathode, 2 mA with a 1.4 V limit to cell voltage, 2.5 F/mol, r.t. [a]Conditions for primary alkylpyridiniums were used. [b]1.2 Equiv of pyridinium salt was used instead of 1.5 equiv.



	Br-29	Br-30	Br-31	Br-32	Br-35	Br-38
S1	22	27	18	17	26	26
S2	26	30	25	21	25	29
S3	31	25	32	23	65	32
S4	32	48	45	35	46	9

	Br-29	Br-30	Br-31	Br-32	Br-35	Br-38
S5	43	24	12	61	25	16
S6	56	34	11	62	50	24
S7	24	34	1	30	33	21
S8	43	12	9	30	19	18

Scheme 8. Multi-dimensional library synthesis

LCAP data for reductive couplings of alkylpyridinium salts and aryl bromides at 35 μmol scale performed on HTe-Chem. Formation of triphenylpyridine was not considered for LCAP determinations. Conditional formatting was applied to indicate the range of LCAPs. Condition for **S1** – **S4**: alkylpyridinium salt (35 μmol, 1 equiv), ArBr (52.5 μmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), **L1** (12 mol %), NaI (1 equiv), DMA (0.1 M), cobalt (+), stainless steel (–), cell potential 0.9 V, 60 °C, 14 h. Condition for **S5** – **S8**: alkylpyridinium salt (52.5 μmol, 1.5 equiv), ArBr (35 μmol, 1 equiv), $NiBr_2$(DME) (10 mol %), tbbpy (12 mol %), $(trpy)_2Ni$ (5 mol %), NaI (1 equiv), DMA (0.1 M), cobalt (+), stainless steel (–), 1 mA, 25 °C, 2.5 F/mol.