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Electrochemically Enabled, Nickel-Catalyzed Dehydroxylative Cross-Coupling of Alcohols with Aryl Halides

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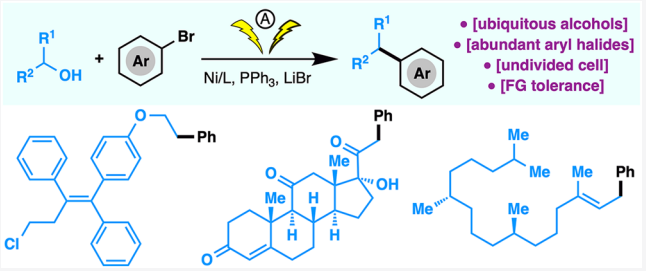
ABSTRACT: As alcohols are ubiquitous throughout chemical science, this functional group represents a highly attractive starting material for forging new C−C bonds. Here, we demonstrate that the combination of anodic preparation of the alkoxy triphenylphosphonium ion and nickel-catalyzed cathodic reductive cross-coupling provides an efficient method to construct C(sp^2)−C(sp^3) bonds, in which free alcohols and aryl bromides—both readily available chemicals—can be directly used as coupling partners. This nickel-catalyzed paired electrolysis reaction features a broad substrate scope bearing a wide gamut of functionalities, which was illustrated by the late-stage arylation of several structurally complex natural products and pharmaceuticals.



1. INTRODUCTION

Developing efficient and practical methods to forge connections between sp^2- and sp^3-hybridized carbons has been and remains a central topic in synthetic chemistry.[1] In recent years, the use of transition-metal-catalyzed reductive cross-couplings between two electrophiles has emerged as a powerful strategy for C(sp^2)−C(sp^3) bond formation[2−11] because these transformations can circumvent the preparation and usage of organometallic reagents, resulting in simple reaction setups and high functional group compatibility. While the seminal contributions in this arena have focused on the use of alkyl halides as C(sp^3) coupling partners (Figure 1A, left),[12−25] the scope has since expanded to include epoxides,[26,27] aziridines,[28,29] alkyl carboxylic acid derivatives (activated esters),[30,31] alkylamine derivatives (pyridinium salts, iminiums, and ammonium salts),[32−38] and alkyl sulfones.[39]

The ubiquity of alcohols across most classes of molecules makes them attractive as potential C(sp^3) coupling partners. However, on account of the relatively strong bond dissociation energy of the C−O bond and low leaving ability of the OH^- group,[40] alcohols are seldom directly employed as alkylating agents in cross-couplings,[41−43] with a notable exception being π-activated allylic and benzylic alcohols.[44−52] Although many alcohol derivatives have been wildly studied in reductive cross-coupling reactions, including alkyl acetates,[53,54] tosylates,[55−58] xanthate esters,[59] mesylates,[60] pivalates,[61] oxalates,[62−64] phosphates,[60] methyl ethers,[65] and chloroformates[66] (Figure 1A, right), such derivatives require preparation step(s) from their alcohol precursors, and the substrate scope is often limited to allylic and benzylic alcohol derivatives. Therefore, it would be synthetically appealing to develop a reaction which can directly harness free alcohols to construct C(sp^2)−C(sp^3) bonds, ideally supporting both π-activated alcohols and alkyl alcohols as starting materials.

Electrosynthesis has been identified as a viable technique for discovery of novel chemical transformations by unconventional mechanistic pathways.[67−74] In 1980, the Ohmori group initially reported that alkoxy triphenylphosphonium ions—the key intermediate of Mitsunobu reaction—could be readily generated by anodic oxidation of triphenylphosphine (PPh_3) with alcohols (Figure 1B),[75] and these alkoxy derivatives could be further used as alkylating agents to form C−X bonds (X = O, N, S, Br, F, etc.),[76−80] with Ph_3PO serving as a leaving group (Figure 1B).[81,82] Considering that two electron equivalents must be donated to the anode during alkoxy triphenylphosphonium ion formation and that two electron equivalents are needed for such cross-electrophile coupling, we explored the idea that the electrochemical oxidation and reductive cross-coupling could be merged as a paired electrolysis reaction to create a novel catalytic platform to achieve direct dehydroxylative cross-coupling (Figure 1C). However, we realized that this proposed paired electrolysis approach for C(sp^2)−C(sp^3) bond formation would pose at least two major challenges:[83−89] (i) the requirement to properly match the innate redox properties of the paired reaction partners and (ii) coordinating the reaction rates for anodic oxidation, cathodic reduction, and the metal catalytic cycle.

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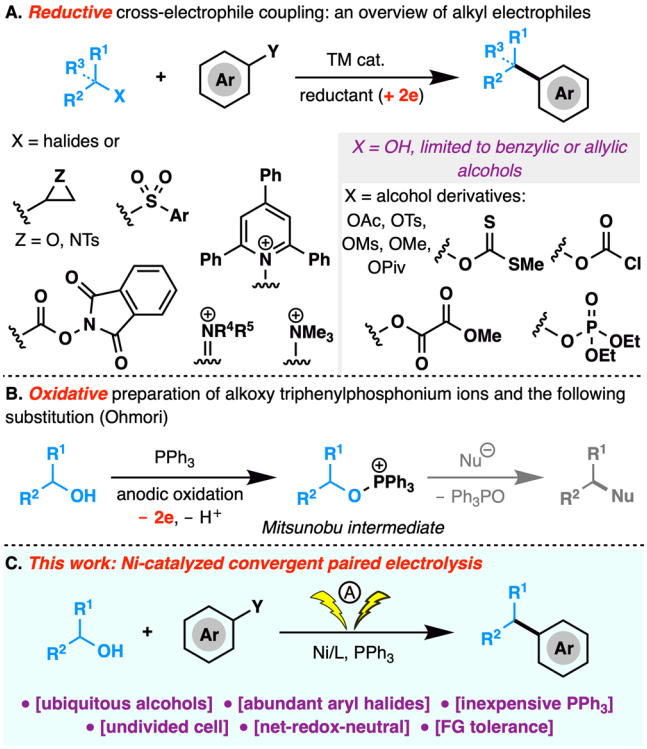


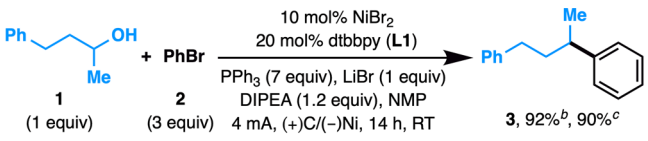
Figure 1. (A) Overview of the alkyl counterparts in reductive cross-electrophile couplings. (B) Electrochemical preparation of alkoxy triphenylphosphonium ions. (C) Nickel-catalyzed electrochemical dehydroxylative arylation.

2. RESULTS AND DISCUSSION

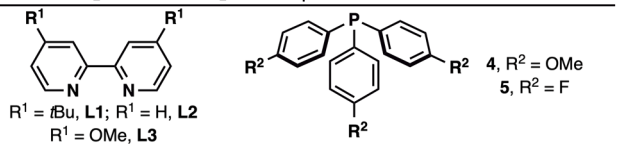
Reaction Optimization. With these considerations in mind, we first examined the proposed cross-coupling by using 4-phenyl-2-butanol (**1**), bromobenzene (**2**), PPh_3, and a wide range of ligated nickel catalysts under various electrochemical conditions. Owing to mechanistic and practical considerations, all of the screening reactions were conducted at room temperature in an undivided cell, and the use of expensive electrode materials was consciously avoided. Table 1 illustrates the optimal reaction parameters alongside an abbreviated picture of the optimization process for these reactions (see the Supporting Information for further details).

Direct control experiments revealed that the coupling reaction did not proceed in the absence of an electric current, nickel catalyst, ligand, or PPh_3 (entries 1–4). We performed a broad evaluation of electric conditions (including electrodes, currents, and electrolytes) and to our delight found that the best yield was provided with an easily available graphite anode and a nickel foam cathode (entry 5). This result has mechanistic significance because to date most reactions for electrochemical formation of $C(sp^2)–C(sp^3)$ bonds utilize sacrificial anodes or reductants to avoid the competitive oxidation of low-valent nickel catalyst.[90−95] In addition, these materials are consistent with our proposed convergent paired electrolysis: they should support a net-redox-neutral transformation. Working at a 0.2 mmol scale, and keeping the total amount of electron equivalent constant, currents ranging from 2 to 4 mA were found to be equally effective (1.1–2.3 mA/cm^2 of graphite, entry 6); increasing the current beyond 4 mA led to lower yields (entry 7). The electrolyte $LiClO_4$ and Et_4NBr could be used in place of LiBr with only a marginal decrease in yields (entries 8 and 9), while other tested electrolytes performed sluggishly.

Table 1. Optimization of the Electrochemical Dehydroxylative Arylation[a]



entry	deviation from above	yield(%)[b]	entry	deviation from above	yield(%)[b]
1	no electricity	0	11	**L2** instead of **L1**	80
2	w/o $NiBr_2$	0	12	**L3** instead of **L1**	88
3	w/o **L1**	0	13	w/o DIPEA	47
4	w/o PPh_3	0	14	PPh_3 (3 equiv)	70
5	RVC instead of graphite	14	15	**4** instead of PPh_3	78
6	2 mA, 28 h	94	16	**5** instead of PPh_3	57
7	6 mA, 9 h	84	17	DMA instead of NMP	89
8	$LiClO_4$ instead of LiBr	86	18	PhBr (2 equiv)	89
9	Et_4NBr instead of LiBr	84	19	PhOTf instead of **2**	92
10	$Ni(COD)_2$ instead of $NiBr_2$	85	20	PhI instead of **2**	63



[a]Reactions were conducted at a 0.2 mmol scale in 3 mL of NMP. [b]Yields were determined by GC/MS with dodecane as the internal standard. [c]Isolated yield.

The inexpensive combination of $NiBr_2$ and bipyridyl ligands (**L1**) provided the most effective catalyst system for this electrochemical dehydroxylative arylation. Notably, using $Ni(COD)_2$ in lieu of $NiBr_2$ resulted in a comparable yield (entry 10), indicating an *in situ* cathodic reduction of Ni(II) to the active catalyst Ni(0) (*vide infra*), with excess PPh_3 likely working as the sacrificial reductant on the anode. Moreover, coupling products were still obtained in satisfactory yields with alternative bipyridine ligands, such as **L2** and **L3** (entries 11 and 12). The presence of a base was essential to neutralize the byproduct HBr, which was detrimental to the yield (entry 13) and would corrode the nickel foam cathode. Of all bases surveyed, DIPEA provided the highest yield. Although 7 equiv of PPh_3 was needed on substrate **1**, note that (i) using 3 equiv of PPh_3 could also produce the desired coupling product **3** in good yield (70%, entry 14); (ii) for many additional substrates, 3 equiv of PPh_3 was used (see Table 2); and (iii) PPh_3 is a nontoxic, air-stable, and low-cost feedstock. Additionally, no improvements in reaction efficiency were obtained via fine-tuning of electron density using various substitutional groups on PPh_3's aryl ring (entries 15 and 16). Of all solvents screened, NMP provided the best yield, although use of DMA also resulted in excellent yields (entry 17). When 2 equiv of PhBr was used, a comparable yield was also obtained (entry 18). Finally, our screening showed that PhOTf and PhI are also viable coupling partners (entries 19 and 20).

Substrate Scope. Having established the optimal conditions for this nickel-catalyzed paired electrolysis, the reaction scope was investigated as shown in Table 2. A range of alkyl primary and secondary alcohols bearing a variety of functionalities, including a phthalimide (**6**), a pyridine (**7**), a ketone (**8**), a carbamate (**9**), a 1,4-dioxane (**11**), a cyano (**12**), ethers (**13**, **14**, **17**), an indane (**15**), and esters (**16**, **18**), were all well accommodated. Moreover, a poly-PEG motif could be successfully incorporated into the aromatic ring (**19**). Additionally, π-activated alcohols including benzylic alcohols (**20**–

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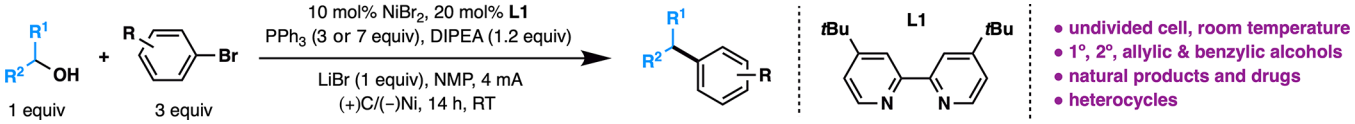
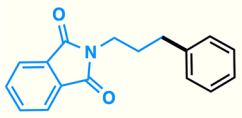
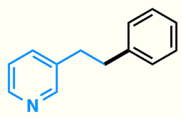
Table 2. Scope of Electrochemical Dehydroxylative Cross-Coupling of Alcohols with Aryl Bromides[a,b]

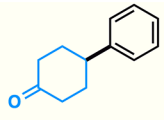


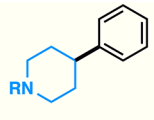
Scope of alcohols

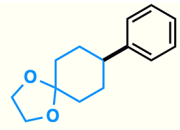
A. Alkyl alcohols

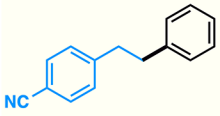

6, 57%[c]

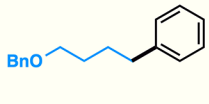

7, 72%[c]

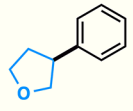

8, 61%[c]

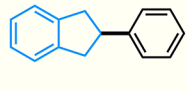

9, R = Boc, 57%[c]
10, R = Ts, 41%[c]

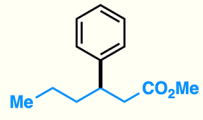

11, 45%[c]

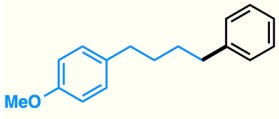

12, 60%[d]

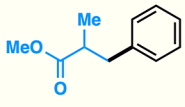

13, 42%[c]

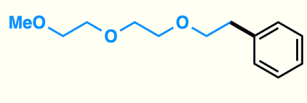

14, 66%[d]

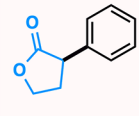

15, 74%[d]


16, 73%[c]

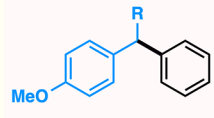

17, 52%[c]

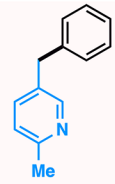

18, 40%[d]

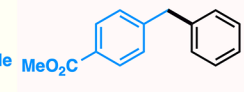

19, 73%[c]

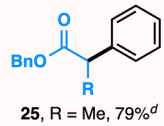

24, 95%[c]

B. π-activated alcohols


20, R = H, 94%[c]
21, R = Me, 63%[d]

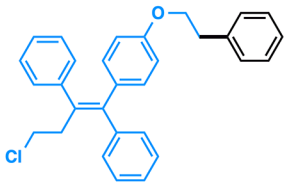

22, 95%[d]

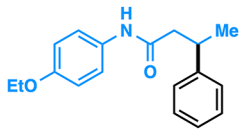

23, 86%[c]

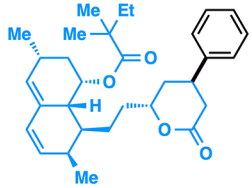

25, R = Me, 79%[d]
26, R = H, 85%[c]

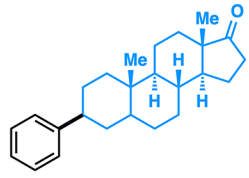

27, 71%[c]

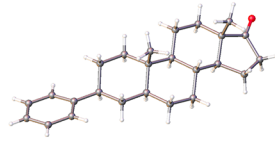
C. Natural products & drugs

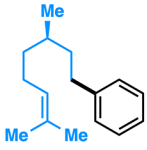

28, 57%[c]
from ospemifene

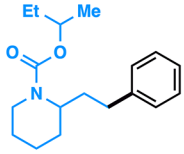

29, 74%[d]
from bucetin

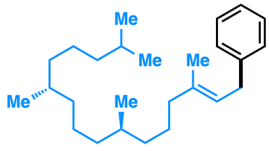

30, 74%[c], d.r. = 1.5:1
from simvastatin

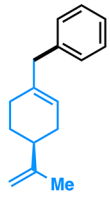

31, 49%[d], d.r. = 1:1
from epiandrosterone

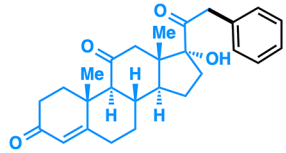

X-ray of one isomer of **31**

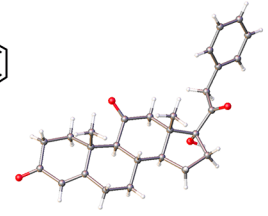

32, 59%[c]
from citronellol


33, 84%[c]
from icaridin

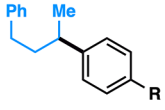

34, 75%[d]
from phytol

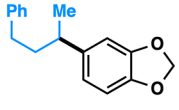

35, 55%[d]
from perillol

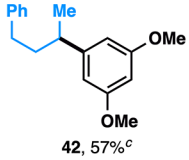

36, 61%[c]
from cortisone

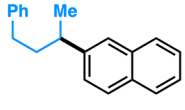

X-ray of **36**

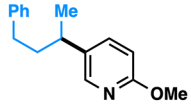
Scope of aryl halides

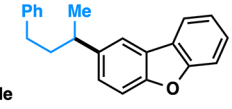

3, R = H, 90%[c]
37, R = CF_3, 60%[e]
38, R = OMe, 61%[d]
39, R = OAc, 41%[d]
40, R = NMe_2, 62%[c]

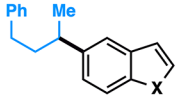

41, 63%[d]

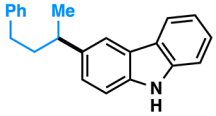

42, 57%[c]

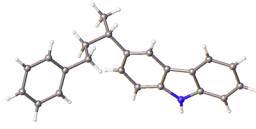

43, 45%[e]


44, 65%[e]


45, 40%[d]


46, X = NH, 43%[d]
47, X = O, 66%[c]


48, 62%[d]


X-ray of **48**

49, 67%[c]

50, 59%[d]

51, 49%[c]

52, 55%[c]

[a]Reactions were conducted on a 0.2 mmol scale. [b]Isolated yield. [c]7 equiv of PPh_3 was used. [d]3 equiv of PPh_3 was used. [e]10 equiv of PPh_3 was used.

23), an allylic alcohol (**27**), and α-hydroxycarbonyl compounds (**24**–**26**) also function in this dehydroxylative arylation with high efficiency. One general trend worth noting is that relatively less sterically hindered alcohols (e.g., **16** and **20**) tended to be more reactive than more sterically hindered alcohols (e.g., **18** and **21**), and tertiary alcohols were not accommodated in the tested reaction context. The result of a competition experiment with differently substituted aliphatic alcohols was also consistent with our observations (Figure 2A).

Hydroxy groups are prevalent in structurally complex drugs and natural products. Accordingly, we further examined this dehydroxylative arylation within various densely functionalized

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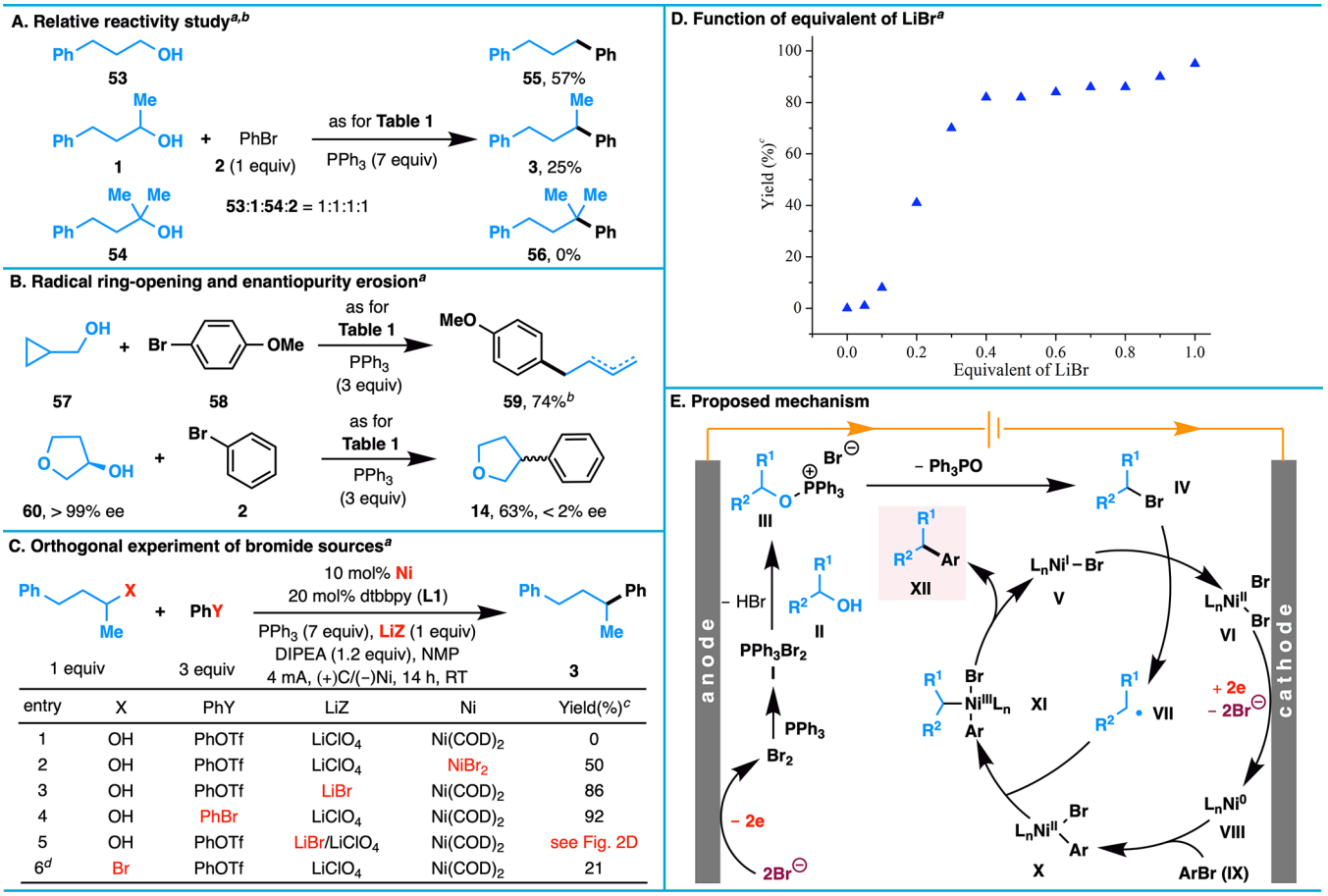

entry	X	PhY	LiZ	Ni	Yield(%)[c]
1	OH	PhOTf	$LiClO_4$	$Ni(COD)_2$	0
2	OH	PhOTf	$LiClO_4$	$NiBr_2$	50
3	OH	PhOTf	LiBr	$Ni(COD)_2$	86
4	OH	PhBr	$LiClO_4$	$Ni(COD)_2$	92
5	OH	PhOTf	LiBr/$LiClO_4$	$Ni(COD)_2$	see Fig. 2D
6[d]	Br	PhOTf	$LiClO_4$	$Ni(COD)_2$	21

Figure 2. (A) Competitive experiment. (B) Mechanistic studies on the generation of alkyl radicals. (C) Investigating the roles of bromide ions. (D) Function of bromide ion equivalent on the yield of **3**. (E) Proposed mechanism for the convergent paired electrolysis. [a]Reactions were conducted at a 0.2 mmol scale. [b]NMR yield. [c]GC yield. [d]With 1 equiv of H_2O and 2.2 equiv of DIPEA.

architectures. As shown in Table 2C, pharmaceuticals and repellents such as ospemifene (**28**), bucetin (**29**), simvastatin (**30**), and icaridin (**33**) were amenable to this reaction, demonstrating the viability of this electrochemical dehydroxylative arylation for late-stage modifications of bioactive molecules. Naturally occurring alcohols such as epiandrosterone (**31**), citronellol (**32**), phytol (**34**), and perillol (**35**) were also competent substrates, enabling access to the desired adducts in synthetically useful yields. Notably, the primary alcohol in the steroid hormone derivative drug cortisone could react smoothly with bromobenzene without disturbing the innate tertiary alcohol, and the structure of product **36** was confirmed by X-ray crystallographic analysis.

We subsequently examined the substrate scope for aryl bromide coupling partners. First, aryl rings that contain functional groups as diverse as a trifluoromethyl group (**37**), ethers (**38**, **42**), an ester (**39**), an amine (**40**), a 1,3-dioxole (**41**), and an extended aromatic ring (**43**) were demonstrated to be viable coupling partners. Second, a series of medicinally relevant and structurally distinct heterocycles including a pyridine (**44**), a dibenzofuran (**45**), an indole (**46**), a benzofuran (**47**), a carbazole (**48**), a benzo[*d*]oxazole (**49**), an indazole (**50**), and a benzo[*d*]imidazole (**51**) were examined as well, and the desired coupling products were successfully afforded in moderate-to-good yields. Of particular note, (i) a vinyl bromide (**52**) was viable in this reaction, and (ii) the free indole (**46**) and free carbazole (**48**) could be used in this cross-coupling directly without protecting the nitrogens, supporting their use as nucleophilic centers for further modifications.

Mechanistic Studies. Interestingly, our substrate scope explorations revealed two losses of stereochemistry at the reaction sites (Table 2, **30** and **31**), a radical ring-opening reaction,[96] and an enantiopurity erosion phenomenon (Figure 2B), which together mechanistically suggested that the alkyl radials were generated though this dehydroxylative arylation process. Given that the C−OH bond did not readily undergo direct homolysis, two potential pathways for the generation of alkyl radicals seem probable: (i) the alkoxy triphenylphosphonium ion may be reduced directly by the low-valent nickel catalyst or perhaps at the cathode through single-electron transfer (SET), potentially generating Ph_3PO and the alkyl radical; (ii) the alkoxy triphenylphosphonium ion may further react with bromide ions—derived from the electrolyte LiBr or the catalyst $NiBr_2$—to form alkyl bromide.[97] Such an *in situ* generated alkyl bromide could undergo single-electron reduction to produce an alkyl radical.

Five lines of experimental evidence added weight to the second pathway: First, given that aryl bromide, $NiBr_2$, and LiBr can be respectively replaced by aryl triflate, $Ni(COD)_2$, and $LiClO_4$ without causing significant yield declines (Table 1, entries 19, 10, and 8), a control experiment was performed in the absence of any bromide source (Figure 2C, entry 1): informatively, no desired coupling product **3** was produced. Second, when using $NiBr_2$ (0.2 equiv of Br^-) in lieu of

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$Ni(COD)_2$, **3** was produced in 50% yield (entry 2), and using LiBr as an electrolyte (1 equiv of Br^-) or PhBr as a coupling partner largely rescued the yield of **3** (entries 3 and 4). Third, a detailed experiment also revealed that the yield of **3** was highly dependent on the equivalent of bromide ion used (entry 5 and Figure 2D). Fourth, when the alkyl bromide was used directly (entry 6, 1 equiv of H_2O was used for the anodic oxidation of PPh_3), the desired coupling product **3** could also be produced, albeit in 21% yield. This relatively low yield was ascribed to the β-elimination of alkyl bromide in the reaction conditions. Finally, the alkyl bromides derived from the alcohols were observed as the major byproducts for some substrates (see the Supporting Information).

Given that the bromide ion was essential for this dehydroxylative arylation, we turned our attention to the anodic oxidation process, since the bromide ion, PPh_3, and the alcohol are all prone to be oxidized on the anode, and the detailed mechanism for the anodic formation of alkoxy triphenylphosphonium bromide remains elusive.[76,79] Interestingly, our cyclic voltammogram investigations revealed that the bromide ion could be oxidized more easily than PPh_3 and alcohol **1** in NMP (oxidative potential: 1.1 , 1.7, and >2.0 V for LiBr, PPh_3, alcohol **1**, respectively, versus Ag/AgCl; see the Supporting Information for details), which demonstrated that Br_2 could be generated first on the anode. Based on the mechanism of the Appel reaction, Br_2 can react with PPh_3 rapidly to produce PPh_3Br_2, which can further couple with an alcohol to generate the alkoxy triphenylphosphonium bromide.

Although further mechanistic studies are clearly warranted, our initial mechanistic investigations, in combination with Weix's elegant demonstration of nickel-catalyzed reductive coupling,[98] lend support for the following proposed mechanism (Figure 2E). The alkyl bromide (**IV**), *in situ* generated from the alcohol via an anodic Appel reaction, can be reduced by Ni(I) complex **V** via a single-electron transfer, thus generating Ni(II) complex **VI** and alkyl radical **VII**. Subsequently, the Ni(II) complex **VI** withdraws two electrons from the cathode to balance the electrochemical equilibrium, producing the Ni(0) complex **VIII**. This Ni(0) complex can diffuse into the reaction solution. Notably, this reductive process also releases two bromide ions, which can be reused in the anodic oxidation, enabling a catalytic Appel reaction. Direct oxidative addition of **VIII** to aryl bromide **IX** can produce the Ni(II) aryl complex **X**. At this point, combination of the alkyl radical **VII** and Ni(II) aryl complex **X** can generate the Ni(III) adduct **XI** that after reductive elimination can afford the desired coupling product **XII** and Ni(I) complex **V**.

An alternative pathway for the generation of the alkyl radical **VII** cannot be fully ruled out: perhaps the alkyl bromide is reduced directly at the cathode via SET,[99−101] and the resulting alkyl radical may be trapped by the Ni(II) complex **X**, a scenario which would ultimately generate the same Ni(III) adduct **XI** (as shown in Figure 2E). Nevertheless, given that (i) the Ni(II) complex could be reduced more readily than the alkyl bromide in reductive cross-couplings and (ii) the possibility that the short-lived alkyl radical generated on the cathode diffuses into the reaction solution to combine with the catalytic amount of Ni(II) complex is low, our current thinking favors the mechanism outlined in Figure 2E. Moreover, since PPh_3 was present in superstoichiometric amounts in this dehydroxylative arylation, a stoichiometric reaction of Ni(II) complex **VI** with Ph_3P in NMP was performed. Interestingly, no ligand exchange between **L1** and PPh_3 was observed by ^{31}P NMR analysis (see the Supporting Information for further details).[102]

3. CONCLUSION

In summary, by merging anodic Appel reaction and nickel-catalyzed cathodic cross-electrophile reaction in an undivided electrochemical cell, we achieved direct arylation of readily available free alcohols. Besides the exceptional substrate generality and functional group compatibility, this one-step paired electrolysis can avoid the use of stoichiometric hazardous CBr_4 or Br_2 in Appel reaction, the isolation of frequently toxic alkyl halides, and the use of stoichiometric Zn or Mn in reductive cross-couplings. Moreover, we anticipate that this cross-coupling reaction is likely to find wide application because of the ubiquity of its building blocks: free alcohols and aryl bromides. Notably, the capacity for electrochemically enabled direct dehydroxylative cross-coupling—using ubiquitous alcohols as $C(sp^3)$ coupling partners—should considerably expand the synthetic utility of organic electrosynthesis. Both the further development and practical application of this reaction, as well as detailed mechanistic studies, are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c13093.

Experimental details, spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 2049256−2049258 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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