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Low-valent cobalt catalyzed direct dehydroxylative cross-coupling of benzyl alcohols with aryl-chlorides

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The direct functionalization of alcohols *via* C–O bond cleavage is a synthetically valuable but challenging transformation. In this work, we report a reductive C(sp^3)–C(sp^2) cross-coupling reaction between benzyl alcohols and a broad range of aryl chlorides. The success of this transformation is attributed to the development of low-coordinate cobalt/bipyridine complexes, which enable the selective conversion of benzyl alcohols into the corresponding diarylmethanes, while minimizing undesired homocoupling of either the benzyl alcohol or aryl chlorides.

Alcohols are among the most abundant and widely distributed functional groups in natural products and bioactive molecules and they also serve as important industrial feedstock chemicals.[1–3] One of the most common functional group interconversions in synthetic chemistry involves the conversion of alcohols to halides and pseudohalides. However, these reactions often require significant time and resources for synthesis, purification and waste management, creating a bottleneck in the efficient production of pharmaceutical compound libraries derived from alcohols.[4–6] Therefore, developing a general and mild approach to functionalize alcohols has received attention[7–24] and their conversion to alkyl halides,[25] sulfonate esters,[26–31] alkyl acetates,[32–35] pivalates,[36,37] methyl ethers,[38] chloroformates,[39] redox-activated intermediates,[40,41] and other derivatives[42–45] has become a crucial strategy to achieve alkylative cross-coupling reactions.

The generation of alkyl radicals through dehydroxylation of alcohols under mild conditions is strategically appealing as alcohols can be directly used as alkylating reagents without the pre-conversion to more activated derivatives.[46–57] However, the strong C–O bond dissociation energy (BDE $\approx$ 95 kcal mol^{-1}) and the high redox potentials of unactivated alcohols make the radical cleavage of the hydroxyl group challenging, often requiring harsh reaction conditions and posing significant difficulties.[58–60] Thus far, Barton-deoxygenation for alkyl C–O bond fragmentation represents the most widely used protocol that effectively generates alkyl radicals by homolytic scission of C(sp^3)–O bonds under photo- or radical-initiator-induced conditions.[61,62]

More recently, alkyl oxalates have been developed as an alternative to the Barton deoxygenation.[63–66] Building on these pioneering studies, several methods have been developed for the deoxygenative activation of alcohols using oxalate esters, enabling the generation of open-shell species for various C–C bond-forming reactions.[67–70]

Shu[67,71–74] and Gong's[75–78] research group independently reported the functionalization of oxalate esters, which were prepared either separately or *in situ* using dialkyl oxalates and stoichiometric amounts of zinc or manganese powder as reducing agents. More recently, this transformation has been accomplished with highly reactive organo-magnesium, lithium, or zinc reagents. However, the use of pyrophoric metal sources in stoichiometric amounts and the need for well-defined dialkylzinc reagents can constitute drawbacks of these methods.[79–82] Consequently, there is growing interest in developing alternative strategies that employ more stable and readily available coupling partners. Such approaches offer an attractive pathway for generating benzyl radicals directly from benzyl alcohol, a more accessible and benign precursor.[83–85] In this context, metal-catalyzed deoxygenative coupling of alcohols with organohalides or pseudohalides has emerged as a direct and efficient method for synthesizing deoxygenative coupling products, such as diarylmethanes, structural motifs that are prevalent in a wide range of bioactive compounds, pharmaceuticals, and functional organic materials.[86–90]

In the current study, we envisioned *in situ* electrochemically generated methyl-oxalate as an activating group, which was pioneered by Utley and co-workers.[91–94] Consistent with their findings, it was observed that methyl oxalate effectively facilitates C–O bond activation.[95] Over the past decade, synthetic electrochemistry has emerged as a powerful and sustainable platform for redox reactions, transforming a broad array of classical transformations into greener and more efficient

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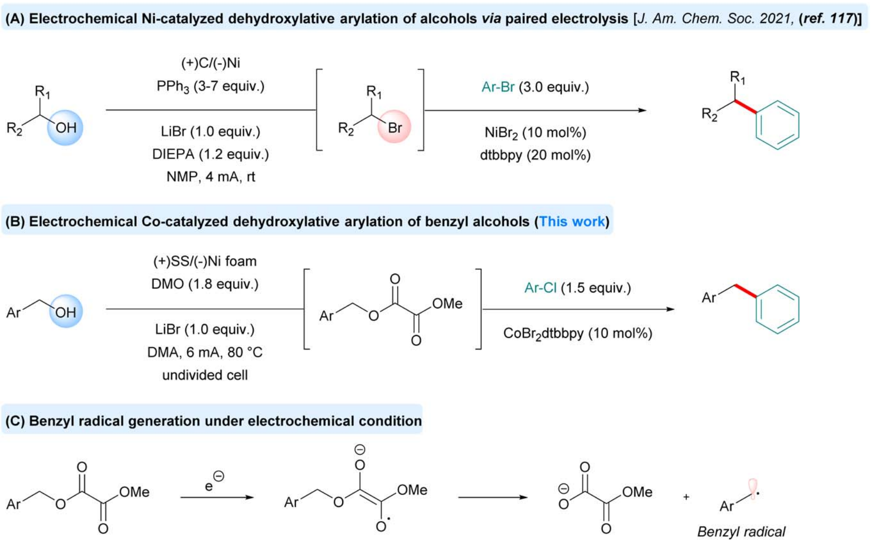


Scheme 1 Electrochemical approaches for dehydroxylative arylation of alcohols.

processes.[96–116] A notable example is the recent work by Li and co-workers, who developed a paired electrolysis protocol that merges the anodic Appel reaction with a nickel-catalyzed cathodic cross-electrophile coupling in an undivided electrochemical cell. This method enables the direct arylation of readily available alcohols with aryl bromides, providing a streamlined and environmentally friendly approach to C–C bond formation (Scheme 1). In addition to its broad substrate scope and excellent functional group compatibility, this method offers a significant advantage by avoiding the use of stoichiometric and hazardous halogenating agents such as CBr_4 or Br_2, commonly employed in the Appel reaction. However, the protocol still requires the use of 3–7 equivalents of triphenylphosphine (PPh_3), which not only increases material cost but also leads to the formation of byproducts and may complicate purification, reducing overall efficiency.[117]

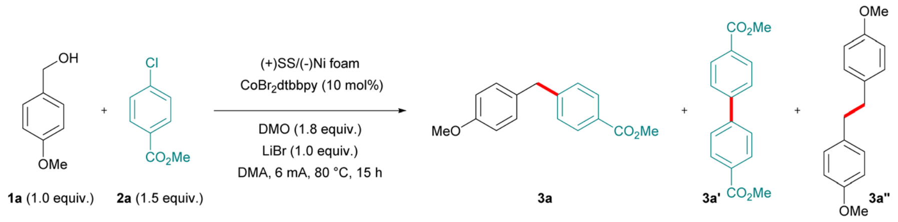
We sought to develop a complementary approach that enables efficient catalysis for $C(sp^2)$–$C(sp^3)$ bond formation under electrochemical conditions. However, the implementation of our proposed electrolysis strategy presented two key challenges. First, it was essential to match the intrinsic redox properties of the paired reaction partners to ensure selective and efficient electron transfer. Second, successful reaction execution required careful adjustment of the rates of the anodic oxidation, cathodic reduction, and the metal-catalyzed cross-coupling cycle. These interdependent processes had to be finely balanced to avoid unproductive pathways and achieve high overall efficiency.

To initiate our study, we began by evaluating earth-abundant transition metal catalysts, such nickel and cobalt with 4-methoxy benzyl alcohol (**1a**) and methyl 4-chlorobenzoate (**2a**) as the standard coupling partners (Table 1).

The reaction was carried out in an undivided electrochemical cell equipped with a stainless-steel anode and a nickel foam cathode, affording the desired product **3a** in 40–45% yield, along with minor side products **3a′** and **3a″**. Subsequent efforts focused on optimizing the reaction parameters to improve efficiency and selectivity. Key variables investigated included the nature of the electrodes (both anodes and cathodes), electrolyte composition, current density, solvent system, and the choice of metal complexes for promoting the deoxygenative reductive cross-coupling reaction[118,119] (see the SI for details, S3–S5). After extensive efforts, the desired product was obtained in 90% isolated yield by using 10 mol% $CoBr_2$(dtbbpy) as the catalyst, 1.8 equiv. of dimethyl oxalate (DMO) as the activator, LiBr as the electrolyte, in DMA solvent (entry 1, Table 1). The use of a nickel catalyst slightly diminished the yield of the diaryl methane product with the formation of a homodimerized side product (entry 2, Table 1). Using different cobalt catalysts led to lower product yields along with some side reactions [**3a′** & **3a″**] (entries 3 and 4, Table 1). Altering the anode or cathode resulted in decreased yields (entries 5 and 6). The use of a non-sacrificial anode along with a sacrificial donor such as Et_3N and TMEDA yielded no product (entries 7 and 8). The reaction was less efficient in solvents such as ACN, DMF and NMP (entries 9–11). Finally, the control experiments demonstrated that all reaction parameters, including the cobalt catalyst, DMO, and electricity are essential for accomplishing this transformation (entries 12–15).

Following the successful optimization, we evaluated the scope and generality of the developed protocol. As shown in Fig. 1 and 2, a series of electronically and sterically diverse benzyl alcohols and aryl chlorides participated in this newly developed cobalta-electrocatalyzed protocol, and the corresponding diaryl methane products were isolated in good to excellent yields. Notably, aryl chlorides as reaction partners provided better yields as compared to aryl bromides and aryl triflates due to homocoupling of both reaction partners (**3a** Fig. 1). Reaction with primary alcohols bearing biphenyl, naphthyl, phenanthrene and fluorene substituents proceeds with good efficiency (**3c–3f**). Benzyl alcohols with methylthio (**3g**), *m*-methoxy (**3h**), di- and trimethoxy (**3i–3j**) reacted equally

Table 1 Optimization of direct deoxygenative cross coupling of benzyl alcohol with aryl chlorides under electrochemical conditions



Entry	Variation from standard conditions[a,b]	3a (%)	3a′ (%)	3a″ (%)
1	Standard conditions	90[c]	Trace	Trace
2	$NiBr_2$dtbbpy (10 mol%)	78[c]	18	Trace
3	$CoBr_2$bpy (10 mol%)	84[c]	10	Trace
4	$CoCl_2(PPh_3)_2$ (10 mol%)	76	Trace	18
5	(+)Fe/(−)Ni foam	70	21	09
6	(+)Zn/(−)Ni foam	77	10	12
7	(+)RVC/(−)Ni foam, Et_3N (3.0 equiv.)	ND	ND	24
8	(+)RVC/(−)Ni foam, TMEDA (3.0 equiv.)	ND	ND	15
9	ACN as solvent	46	21	24
10	DMF as solvent	77[c]	20	15
11	NMP as solvent	72	15	ND
12	w/o $CoBr_2$dtbbpy	ND	ND	45[c]
13	w/o DMO	ND	70	10
14	w/o electricity	ND	ND	ND
15	Reaction at rt	ND	78[c]	10

[a] Standard conditions: **1a** (0.4 mmol), **2a** (0.6 mmol), $CoBr_2$dtbbpy (10 mol%), DMO (1.8 equiv.), LiBr (1.0 equiv.), DMA, (4.0 mL), constant current i = 6 mA, 80 °C, 15 h. [b] GC-FID yield using dodecane as the internal standard. [c] Isolated yield. ND = not detected.

well under the reaction conditions. Importantly, free phenolic hydroxyl groups at various positions as well as the dimethylamino group were also well tolerated. The chemoselectivity of the transformation was found to be good as illustrated by the tolerance of functional groups including fluoro (**3p**, **3r**), trifluoromethyl (**3q**), trifluoromethoxyl (**3s**) and cyano (**3u**) moieties. Furthermore, reactive functional groups such as fluoro or chloro substituents or boronic esters were tolerated, providing opportunities for further late-stage functionalization (**3r**, **3s**, **3t**, and **3v**). In addition, the reaction also proceeds with good efficiency using heterocyclic benzyl alcohol substrates containing furan, thiophene, pyridinyl, benzofuran, and indole motifs (**3w–3ab**). Notably, cinnamyl alcohol as a substrate also provided 1,1′-(1-propene-1,3-diyl)dibenzene (**3ac**) in 72% yield. 1,4-benzenedimethanol also underwent the reaction, affording the desired product in moderate yield (**3ad**).

We next turned our attention to evaluate the scope of aryl chlorides (**2**), using 4-methoxy benzyl alcohol (**1a**) as a model substrate (Fig. 2). As anticipated a variety of aryl chlorides having various steric and electronic substituents at different positions of the aryl ring were well tolerated under the standard reaction conditions. Substituents such as deuterium (**3ae**), methyl (**3af**), ^{t}Bu (**3ag**), biphenyl (**3ah**), naphthyl (**3ai** and **3aj**), and methoxy (**3ak**) afforded diarylmethanes in good to excellent yields. Halo-substituted aryl halides such as fluoro (**3al**) and trifluoromethyl (**3m**) derivatives, resulted in 81% and 87% yields respectively. Of note, the method also allowed the formation of monosubstituted chloro-diaryl methane (**3an**) from a 1,4-dichloroarene substrate which can be used as a handle for further functionalization.

Furthermore, substituents such as cyano (**3ao**), esters (**3ap–3as**), aldehyde (**3at**), alkene (**3au**), and aliphatic and aromatic ketones (**3av** and **3aw**), also proved efficient. In addition, heteroaromatic chlorides with groups such as thiophene (**3ax**), pyridine (**3ay** and **3az**), dibenzofuran (**3aaa**), carbazole (**3aab**) provided the corresponding products in good to moderate yields. Notably, the current methodology is suitable for late-stage functionalization as chloro compounds derived from L-menthol, clofibrate, fenofibrate and furegrelates reacted smoothly, affording the corresponding products (**3aac–3aag**) in good to moderate yields.

To gain insights into the reaction mechanism, a series of control experiments were conducted (Fig. 3). First, the formation of the oxalate ester intermediate was confirmed under the optimized reaction conditions. The conversion of 4-methoxybenzyl alcohol (**1a**) to oxalate ester (**4**) was sluggish at room temperature but proceeded efficiently at 80 °C. In the presence of the cobalt catalyst, the reaction afforded oxalate ester (**4**) in 36% yield and the deoxygenative homocoupled product (**3a″**) in 42% yield. In contrast, in the absence of cobalt, the oxalate ester (**4**) was obtained in 27% yield and **3a″** in 34% yield (Fig. 3, equation (A)). The enhanced formation of the oxalate ester in the presence of cobalt suggests that the cobalt catalyst facilitates transesterification. In another experiment the use of separately prepared oxalate ester (**4**) under standard reaction conditions led to the exclusive formation of deoxygenative homocoupled product (**3a″**) (Fig. 3, equation (B)). The reductive cross coupling reaction of the oxalate ester with aryl chlorides under standard reaction conditions afforded the cross-coupled diaryl methane compound (**3a**) in 77% yield (Fig. 3, equation (C)). Upon adding an excess amount of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxy), only a trace

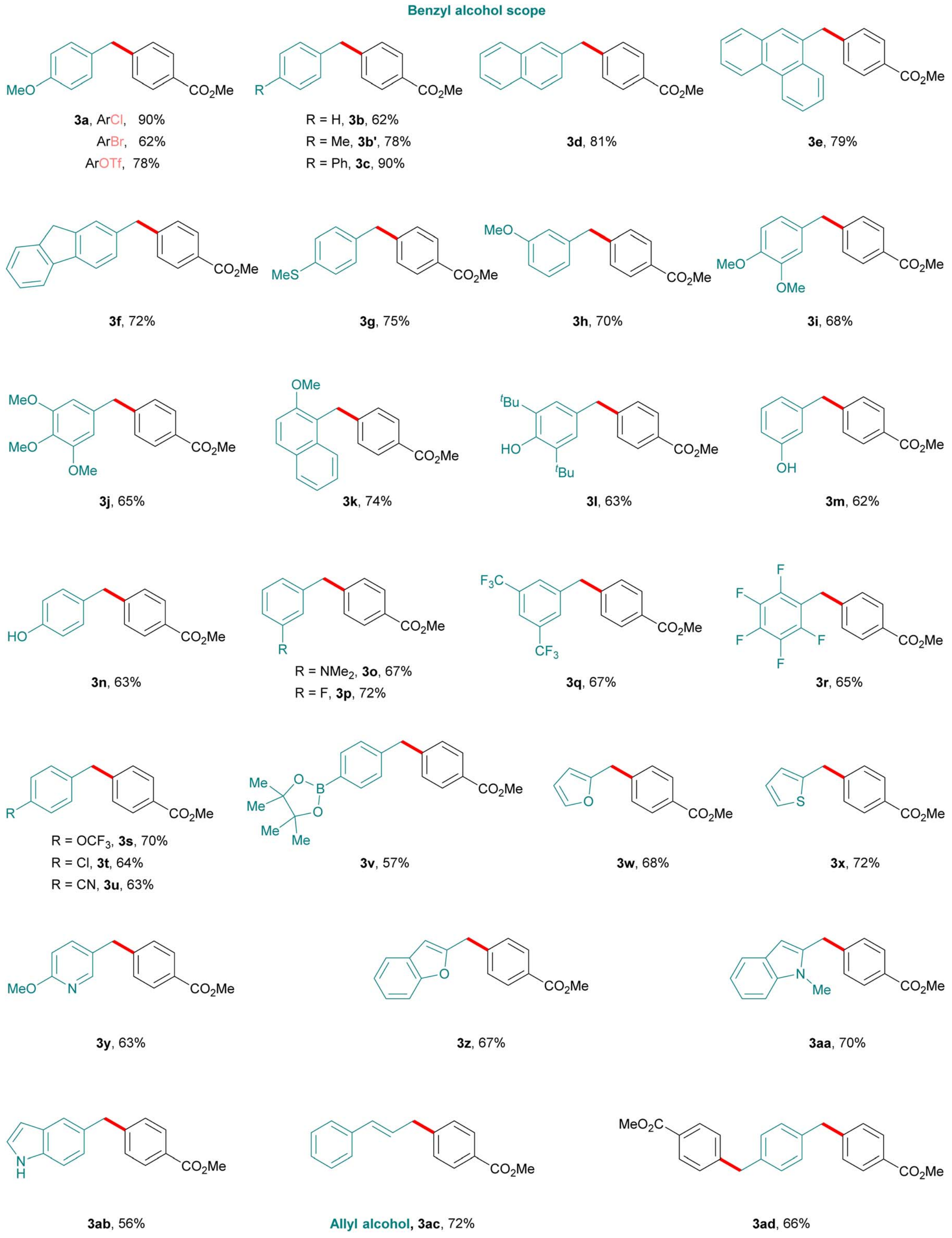


Fig. 1 Benzyl alcohol scope. Reaction was performed with **1a** (0.4 mmol), **2a** (0.6 mmol), $CoBr_2$dtbbpy (10 mol%), DMO (1.8 equiv.), LiBr (1.0 equiv.), DMA, (4.0 mL), constant current *i* = 6 mA, 80 °C, 15 h.

amount of product (**3a**) was detected (Fig. 3, equation (D)). Finally, the reaction with 1,1-diphenylethylene afforded the benzyl radical addition product (**6**) in 27% isolated yield (Fig. 3, equation (E)). These experiments indicate that a benzyl radical intermediate is involved in the reaction pathway, and the benzyl alcohol serves as the radical precursor *via* oxalate ester formation for the cross-coupling reaction. Notably, when 4-methoxybenzyl chloride was employed instead of 4-methoxybenzyl

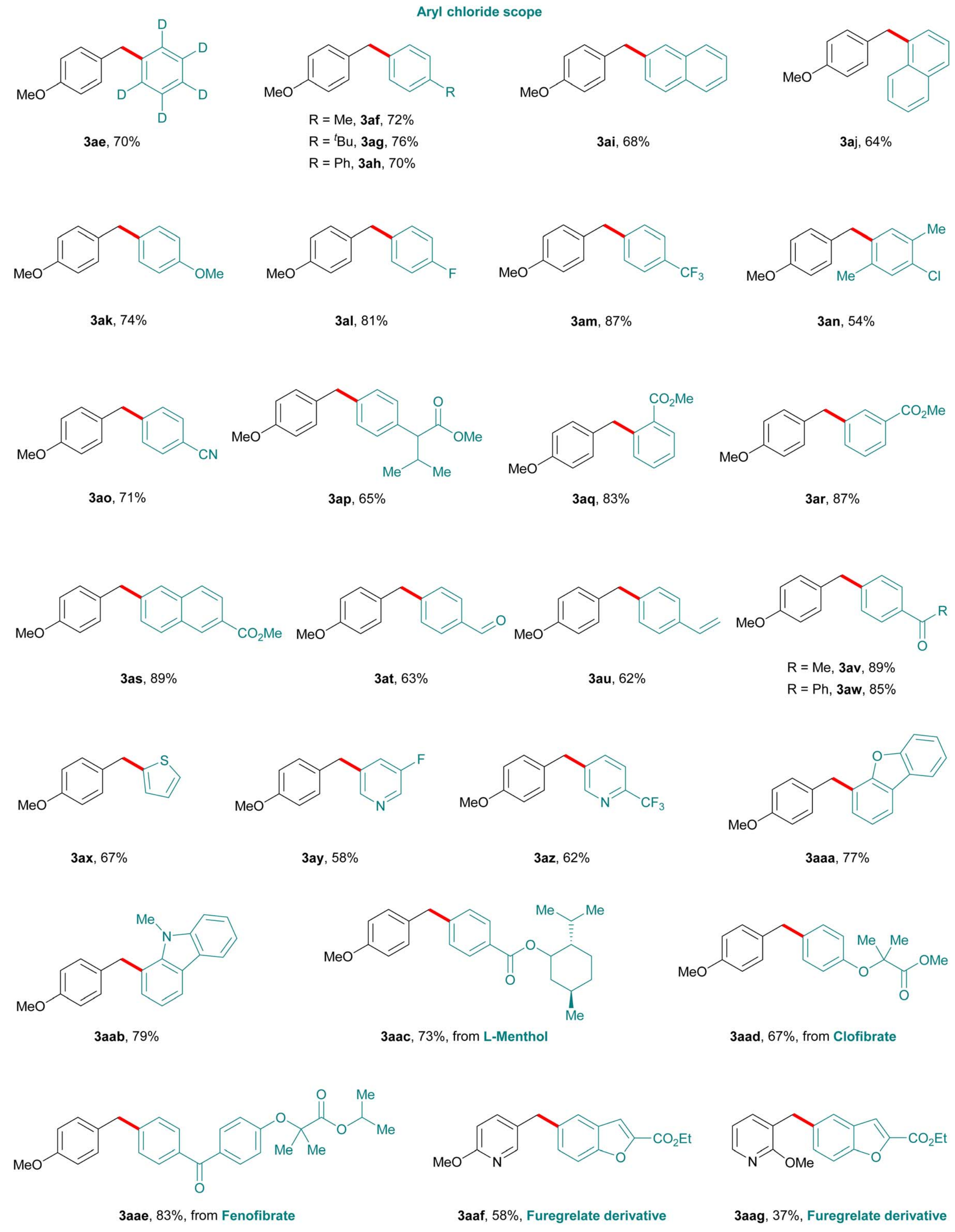


Fig. 2 Aryl chloride scope. Reaction was performed with **1a** (0.4 mmol), **2a** (0.6 mmol), $CoBr_2$dtbbpy (10 mol%), DMO (1.8 equiv.), LiBr (1.0 equiv.), DMA, (4.0 mL), constant current $i = 6$ mA, 80 °C, 15 h.

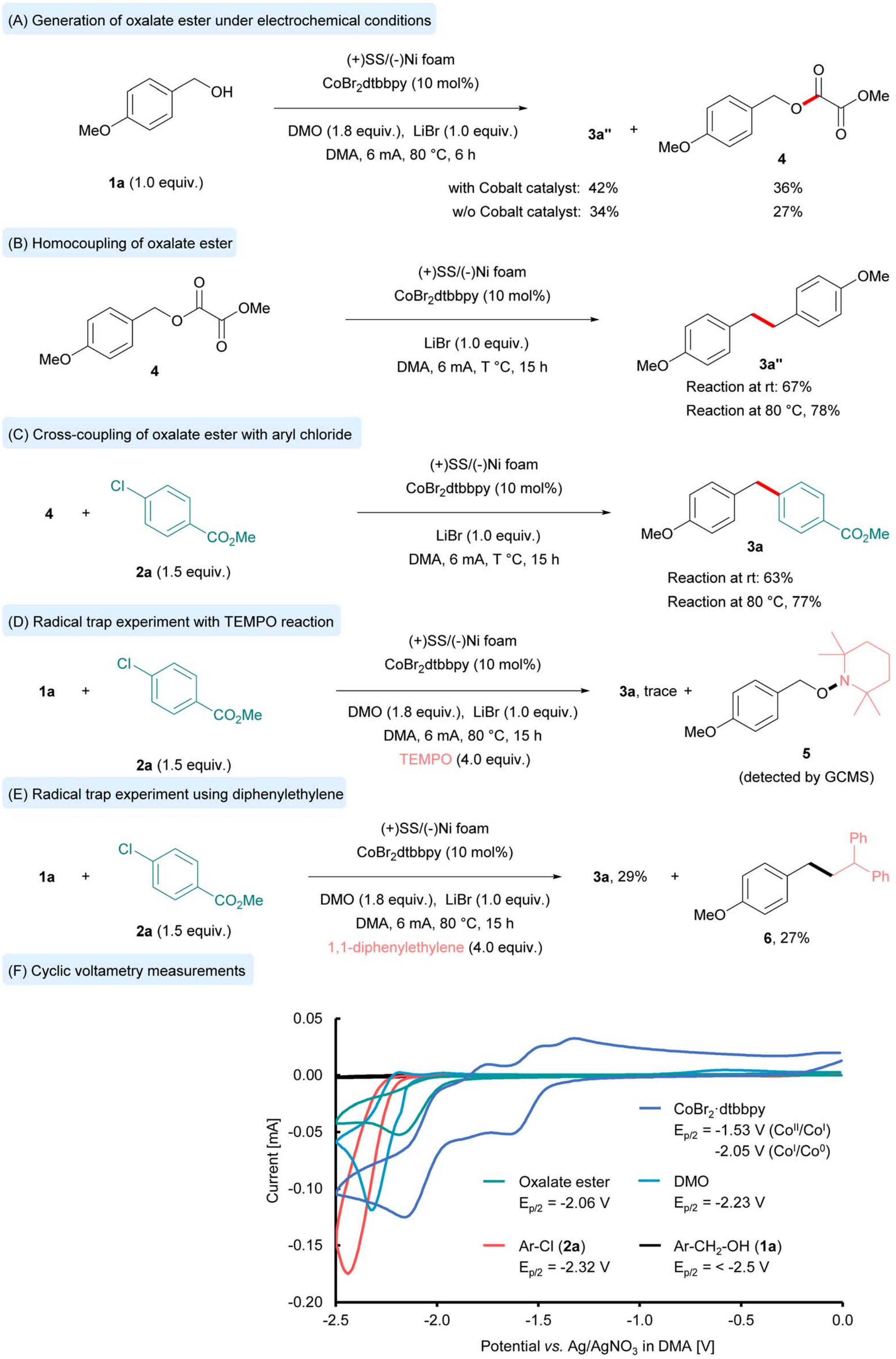


Fig. 3 Mechanistic studies.

alcohol (**1a**) with methyl 4-chlorobenzoate (**2a**), only a trace amount of the cross-coupled product was obtained (see detailed control experiments in the SI, S-7). We subsequently conducted cyclic voltammetry (CV) measurements in DMA, as illustrated in Fig. 3 (equation (F)). The reduction potential of 4-methoxybenzyl alcohol (**1a**) was ascertained to be below −2.5 V *vs.* Ag/AgNO$_3$, rendering its reduction unfeasible under the present protocol. Conversely, the reduction potentials of methyl 4-chlorobenzoate (**2a**), DMO, and oxalate ester were −2.32 V, −2.23 V, and −2.06 V *vs.* Ag/AgNO$_3$, respectively. These findings

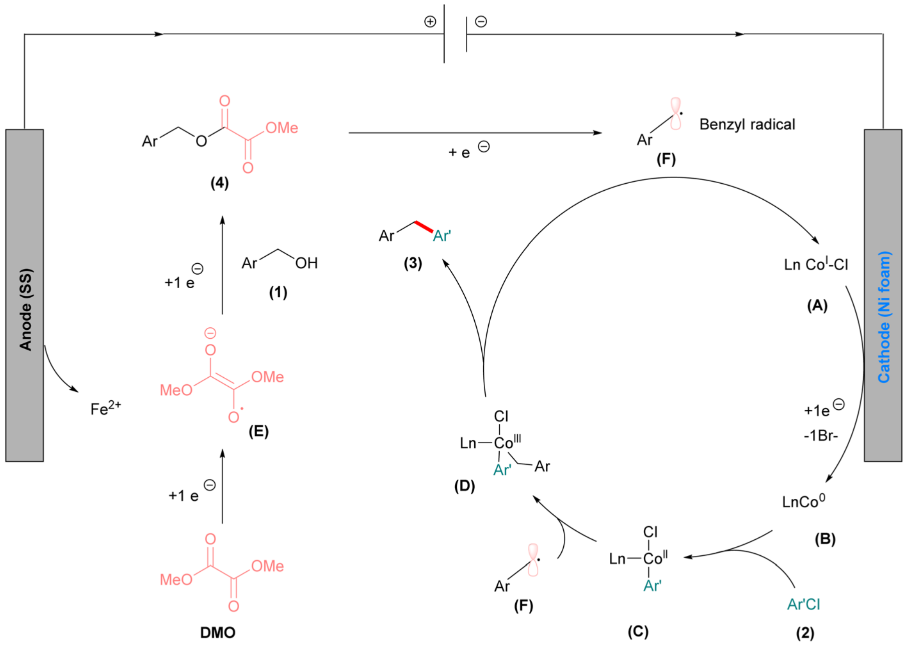


Fig. 4 Plausible reaction mechanism of the cobalt catalyzed C–C bond forming reaction.

suggest that DMO is initially reduced at the cathode, leading to the *in situ* formation of the oxalate ester. This oxalate ester can subsequently undergo further reduction at the cathode, yielding the benzylic radical. We also determined the reduction potential of the cobalt catalyst ($CoBr_2 \cdot dtbbpy$), observing two reduction peaks. These peaks correspond to the Co^{II}/Co^{I} reduction (−1.53 V *vs.* $Ag/AgNO_3$) and the Co^{I}/Co^{0} reduction (−2.05 V *vs.* $Ag/AgNO_3$). Given that the reduction of Co^{I} to Co^{0} is more facile than that of DMO and aryl chloride (**2a**), we postulate that Co^{0} is produced during the electrochemical reaction. This suggests that aryl chloride more readily undergoes oxidative addition with Co^{0} than direct reduction.

Based on the gathered experimental evidence and literature reports[72,75,93,120–122] we proposed a reaction mechanism that accounts for the formation of the observed product (Fig. 4). Initially, the pre-catalyst $CoBr_2$dtbbpy undergoes cathodic reduction to form the catalytically competent low valent Co^{0} species (**B**) *via* two electron transfer processes. The low valent cobalt species then undergoes oxidative addition with aryl chloride (**2**) that leads to formation of a Co^{II} intermediate (**C**). In parallel, under electrochemical conditions, DMO undergoes single electron reduction to afford the radical anion intermediate (**E**). The subsequent proton exchange process yields the alcohol anion and the *trans*-esterification with benzyl alcohol (**1**) leads to the formation of the oxalate ester (**4**) intermediate. The oxalate ester (**4**) immediately undergoes one electron reduction, generating the reactive benzyl radical (**F**). The generated benzyl radical (**F**) now participates in the catalytic cycle, resulting in the formation of the Co^{III} intermediate (**D**). Finally intermediate (**D**) undergoes reductive elimination to afford the diarylmethane (**3**) along with Co^{I} species that again enters the next catalytic cycle. The alternative pathway of benzyl radical addition to the Co^{0} complex (**B**) to afford the Co^{I} intermediate followed by oxidative addition of aryl chloride to generate the Co^{III} intermediate (**C**) cannot be completely ruled out.

In conclusion, we present the first example of *in situ* generated *O*-benzyl oxalate ester pronucleophiles derived from abundant benzyl alcohols in C(sp^3)–C(sp^2) cross-coupling reactions by the strategic merger of electrochemistry with cobalt catalysis. The method relies on the electrochemical generation of benzyl radicals *via* selective cleavage of the oxalate ester, employing dimethyl oxalate, a low-molecular-weight, inexpensive, and commercially available reagent as an effective activator under mild electrochemical conditions. A key feature of this protocol is its ability to selectively suppress competing radical dimerization pathways, leveraging the inherent chemoselectivity of the electrocatalytic cobalt catalyst. Notably, the method circumvents the use of stoichiometric metal reductants such as Zn or Mn, or costly reagents like hydrosilanes, which are often employed in reductive cross-coupling reactions. By utilizing alcohols as unconventional radical precursors, this approach opens a new avenue for C (sp^3)–C (sp^2) bond-forming chemistry, expanding the synthetic utility of readily available alcohols beyond their traditional use in sustainable and modular C–C bond construction.

Author contributions

P. S. S., V. S. S., and M. R. conceived and designed the experiments. P. S. S. and V. S. S. conducted the experiments, analyzed the data and wrote the manuscript, while M. R. supervised the project and manuscript preparation.

Conflicts of interest

The authors declare no competing financial interests.

Data availability

Experimental procedures and characterization of the new compounds are available in the supplementary information (SI). Supplementary information is available. See DOI: **https://doi.org/10.1039/d5sc05919d**.

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