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Catalyst-Dependent Direct and Deoxygenative Coupling of Alcohols by Convergent Paired Electrolysis

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Abstract

Developing a general and mild approach upgrading alcohols to high value products is a hot topic in synthetic chemistry, since alcohol is one of the most abundant raw chemicals. Specifically, direct coupling and deoxygenative coupling of alcohols are the two main approaches for the functionalization of alcohols to afford structurally diverse products, and it receives considerable attention. Despite significant advances in the field, there still remains great challenge to develop a general approach accommodating both coupling reactions, as they commonly involve distinct pathways. Herein, we report an electrochemical approach for the direct coupling and deoxygenative coupling of alcohols with fluorenones. Under paired electrolysis, this catalyst-dependent protocol gives a divergent access to diols and tertiary alcohols. Moreover, the synthetic utility of 9H-fluoren-9-ol products has been demonstrated in the synthesis of organic luminophores, phenanthrol, phenanthridine and amino alcohol. The present approach exhibits some impressive features: a) catalyst-dependent selectivity; b) excellent functional-group tolerance (156 examples); c) mild conditions; d) good scalability (~20-gram scale).
Keywords
Paired electrolysis, Deoxygenative coupling, Direct coupling, Catalyst-dependent selectivity

Introduction

Alcohol is one of the most abundant industrial feedstock chemicals (>10^6), and it also widely distributes in natural products (61.1%) and bioactive molecules (13.6%) (Scheme 1a). Consequently, developing a general and mild approach to functionalize alcohols has received tremendous attention. Among various transformation, cross-coupling reaction of alcohols can be readily used for the construction of C-C bonds enabling a promising approach for diversification of alcohols as well as late-stage modification of bioactive molecules. The cross coupling reaction of alcohols could proceed via C-H and C-O cleavage, which are known as direct coupling and deoxgenative coupling (Scheme 1b). Direct coupling of alcohols conventionally proceed through dehydrogenative and borrowing-hydrogen approaches, which involves stoichiometric oxidant and transition metals. On the other hand, deoxygenative coupling of alcohols allows an appealing opportunity to using alcohols as alkylating reagents, yet it receives far less attention. The difficult C(sp^3)-O cleavage step is a notorious challenging issue in the reaction. Although some homolytic deoxgenation methods are well known (Barton–McCombie reaction), most of these methods has to transform hydroxyl groups into activating groups, which limit the practical applications. These two coupling reactions offer an attractive opportunity to access structurally diserve products. However, these reactions commonly proceed through two distinct pathways, and it is difficult to develop a general approach for the both reactions. Recently, MacMillan, the pioneer of photoredox catalysis, reported a novel metallaphotoredox strategy for the both direct and deoxgenative arylation of alcohols in a redox-neutral approach (Scheme 1c). Despite of the notable progress, there still remains great challenge to develop a general approach for the both coupling reactions of alcohols, featuring with mild condition, broad substrate scope, good scalability and divergent selectivity.
Synthetic electrochemistry has emerged as a ‘green’ platform for redox reactions, and the advances in the field have revolutionized broad range of conventional reactions. Particularly, paired electrolysis technology, which fully utilizes both half-electrode reactions (anodic oxidation and cathodic reduction), is highly energy-efficient, and represents an ideal merging for redox-neutral reactions (Figure 1a). Exploiting the potential of electrochemistry in organic synthesis forms a major part of our own ongoing research interest. In this context, we sought to develop an electrochemical approach for both direct and deoxgenative coupling reaction of alcohols with paired electrolysis technology.

In the convergent paired electrolysis, two intermediates are commonly generated and slow-released from separate electrodes (anode and cathode). Decomposition and homo-coupling of the intermediators are the main side reaction (Figure 1a). To avoid the undesired side reactions, generating persistent intermediates (radical or ion) at the electrode is crucial. 9-Fluorenone (FL) derivatives as anolyte redox materials have been extensively explored in redox flow batteries (Figure 1b). The radical anion (FL−) and dianion (FL−2) arising from 9-fluorenone exhibits good stability and versatile reactivity. Moreover, fluorene and 9H-fluoren-9-ol as privileged scaffolds have been extensively explored in the synthesis of organic light emitting materials, biaryl...
atropisomers\textsuperscript{49-50} and spiro molecules\textsuperscript{51}. In this context, 9-fluorenone is selected as a coupling partner to investigate the electrochemical cross-coupling reaction of alcohols, and access synthetically useful products (Figure 1c). With two catalytic systems, we herein demonstrate that the electrochemical protocol is compatible with the both coupling reactions of alcohols with fluorenes, providing a general platform to diversification of alcohols. 4-Hydroxy-2,2,6,6-tetramethyl-piperidine 1-oxyl (TEMPOL) is reported as a robust catalyst for the direct coupling of alcohols with fluorenones, giving a general access for non-symmetric 1,2-diols. Alternatively, the catalytic system of I/PPh\textsubscript{3} enables a mild approach for deoxygenative coupling of alcohols to afford broad range of tertiary alcohols. As a consequence, this catalyst-dependent transformations can serve as appealing alternatives for the conventional cross-pinacol coupling\textsuperscript{52-54} and the Grignard reaction\textsuperscript{55}. Furthermore, these novel products have been demonstrated as versatile building blocks in the construction of organic luminophores, phenanthrol, phenanthridine and amino alcohol. Taken together, our present approach exhibits some impressive features: a) catalyst-dependent selectivity; b) excellent functional-group tolerance (156 examples); c) ambient atmosphere, metal-free condition; d) good scalability (\~20-gram scale).
Figure 1. Background for paired electrolysis. a) Advantages and challenges of paired electrolysis in organic synthesis. b) Application of 9-fluorenone in redox flow batteries. c) Electrochemical cross-coupling reaction of alcohols.

Experimental Methods

General procedure for direct coupling reaction of alcohol

An undivided cell was equipped with a magnet stirrer, lead plate (1.8 * 1.5 cm²), graphite rod (0.6 * 10 cm), as cathode and anode, respectively (the electrolysis setup is shown in Fig. S1). The substrate 9-fluorenone 1a (180 mg, 1 mmol), benzyl alcohol 2a (208 µL, 2 mmol), TEMPOL (34 mg, 0.2 mmol) and "Bu4NOAc (301 mg, 1 mmol)
were added to the solvent CH$_3$CN/EtOAc (3/7 mL). The resulting mixture was allowed to stir and electrolyze at constant current condition (25 mA, $J = 9.3$ mA cm$^{-2}$) at 50 °C for 5 hours. Then the volatile solvent was removed with a rotary evaporator. The residue was purified by column chromatography (PE/ EA= 6/1-3/1) on silica gel to afford the desired product 3a (265 mg) in 92 % yield.

**General procedure for deoxygenative coupling reaction**

An undivided cell was equipped with a magnet stirrer, lead plate (1.8 * 1.5 cm$^2$), graphite rod (0.6*10 cm), as cathode and anode, respectively (the electrolysis setup is shown in Fig. S1). The substrate 9-fluorenone 1a (180 mg, 1 mmol), benzyl alcohol 2a (208 µL, 2 mmol), PPh$_3$ (787 mg, 3 mmol), $n$Bu$_4$NI (55 mg, 0.15 mmol) and $n$Bu$_4$NClO$_4$ (342 mg, 1 mmol) were added to the solvent CH$_3$CN/EtOAc (3/7 mL). The resulting mixture was allowed to stir and electrolyze at constant current condition (20 mA, $J = 7.4$ mA cm$^{-2}$) at 50 °C for 5 hours. Then the volatile solvent was removed with a rotary evaporator. The residue was purified by column chromatography (PE/ EA= 20/1-15/1) on silica gel to afford the desired product 4a (163 mg) in 60 % yield.

**Results and Discussion**

**Reaction Optimization**

We began our investigation of the electrochemical coupling of benzyl alcohol (2a) and 9-fluorenone (1a) by using a lead plate as cathode in the mixed solvent of acetonitrile and ethyl acetate (Scheme 2). It was found that the mixed solvent and Pb cathode could significantly suppress the side reaction, transfer hydrogenation, in the cross-coupling reactions (Table S1). To further optimize reaction conditions, various aminoxyl radical catalysts$^{56-59}$ and halide mediators were screened in the electrochemical direct coupling (Scheme 2a) and deoxygenative coupling of alcohols (Scheme 2b), respectively. TEMPO (cat 1) was identified as the optimal catalyst to deliver the 1,2-diol product 3a with 92% yield. Replacing the hydroxy group with H (cat 2), NHAc (cat 3) and NH$_2$ (cat 4) failed to give any appreciable yields of product. Bicyclic aminoxyl catalyst (cat 5) did afford a moderate yield (72%), however the absence of catalyst caused a dramatic decrease in yield (38%).
These results indicated that the aminoxyl radical catalyst is crucial for the reaction to proceed efficiently. In the electrochemical deoxygenative coupling, various halide mediators were evaluated to promote the key step: anodic deoxygenative halogenation of alcohols (Appel reaction).\textsuperscript{15,60-61} It was determined that iodine mediator (\textsuperscript{15}Bu\textsubscript{4}NI) gave the best yield, possibly arising from the better leaving group ability of the iodine atom when compared to chlorine and bromine atoms. In the absence of halide mediator, no desired product was observed, which confirmed that the electrochemical halogenation of alcohols is an essential step for the deoxygenative coupling of alcohols. It is worth mentioning that replacing benzyl alcohol with toxic halide substrates (BnCl, BnBr, BnI) ceased the reaction directly (Scheme 6). These results highlighted the superiority of the paired electrolysis approach.

![Diagram of the reaction](attachment:image.png)

### Scheme 2. Optimization of electrochemical cross-coupling reaction of alcohols

#### Substrate Scope

With the optimized reaction conditions in hand, we were poised to investigate the substrate generality of the electrochemical direct coupling with various alcohols and fluorenone derivatives (Scheme 3). Initially, benzyl alcohols with various substituents (3a-3ah), fused rings (3ai-3am) and heterocycles (3an-3ar) were
subjected to the optimal conditions. It was found that this electrochemical protocol is widely applicable, and insensitive to the electronic and steric properties or position of substituents. It is particularly exciting that a wide array of functional groups was well tolerated in the transformation, including thioether (3n-3o), amide (3p), nitrile (3q), ester (3r), alcohol (3s, 3ab) and pyridyl (3an-3ao); these functional groups are challenging or simply inaccessible to the conventional pinacol coupling reaction. In the cases of 3s and 3ab, monoco-coupling products were observed with high selectivity. Subsequently, a broad range of allyl (3as-3bc), propargyl (3bf-3bg) and alkyl (3bd-3be, 3bh-3bs) alcohols were employed to further demonstrate the superiority of the electrochemical approach. In the conventional pinacol coupling reaction, the corresponding α,β-unsaturated aldehydes commonly lead to mixed coupling products due to the presence of multiple reactive sites, and aliphatic aldehydes with a more negative reduction potential proved to be less reactive substrates. Examination of the radical clock precursor cyclopropylmethanol as substrate afforded the corresponding diol 3bn as single product, providing supporting evidence for a non-radical pathway. The synthetic utility of the electrochemical direct coupling was also highlighted by the late-stage functionalization of some natural products or their derivatives, such as solanesol (3bb), farnesol (3bc), (-)-β-citronellol (3bd) and Boc-D-proline (3br). Notably, methanol and ethanol, which represent renewable C1 and C2 feedstock, were amenable to the reaction conditions and afforded the desired alkylated products, albeit with low yields (3bh-3bj). Additionally, the scope of fluorenones was also examined through a variety of substituents, and the diol products (3bt-3cj) were observed with moderate to good yields. Finally, other ketones were further investigated. To our delight, benzophenone proved to be successful in the reaction giving product 3ck with 51% yield, whereas other substrates (1t-1w) failed to give corresponding coupling products. These results could be interpreted with the stability of the intermediates in the reaction. Diarylmethyl radicals/anions arising from fluorenone or benzophenone are more stable than the counterparts of aliphatic ketone or acetophenones.
Scheme 3. Substrate scope of direct coupling of alcohols with fluorenones. Unless otherwise noted, the reaction was performed with the conditions: fluorenone 1 (1 mmol), alcohol 2 (2 mmol), °Bu₄NOAc (1 mmol), cat 1 (0.2 mmol), graphite rod anode, lead plate cathode, constant current (25 mA), 5 hours (4.7 F/mol), CH₃CN (3 mL), EtOAc (7 mL), undivided cell, 50 °C. Using 1,8-Diazabicyclo[5.4.0]undecl-7-ene DBU (2 mmol) as an extra additive.
Having surveyed the generality of direct coupling reaction, we turned our attention to the development of an electrochemical deoxygenative coupling of alcohols. A wide variety of alcohols and fluorenones were tested with the optimized reaction conditions (Scheme 4). Benzyl, allyl and propargyl alcohol proved to be effective alkylating agents to give the corresponding tertiary alcohols (4a-4ar) in moderate yields. However, aliphatic alcohols failed in the reaction, owing to their low reactivity (in the deoxygenative halogenation process) and undesired Wittig reaction. Gratifyingly, sterically encumbered substrates anthracen-9-ylmethanol (4ac) and Adapalene derived alcohol (4ab) were well tolerated in this protocol, although diminished yields were observed. Remarkably, secondary alcohols were suitable to give the desired products (4ap, 4ar, 4as), but with lower yields, which might be induced by steric hindrance. Significantly, the cyclopropyl group was well preserved in the reaction to afford 4as as exclusive product, suggesting an ionic pathway in the transformation. Deuterated benzyl alcohol underwent the deoxygenative coupling to afford the corresponding product (4aq) without erosion of deuterium content. Several fluorenones with varied substituents were also compatible with the reaction to afford the products (4at-4bo) with slightly lower yields. Notably, sterically hindered (4bi-4bj) and heterocyclic (4bo) fluorenones could be alkylated with benzyl alcohol in the electrochemical transformation. Nevertheless, replacing fluorenone with other ketones (1s-1w) directly shut down the reaction.
Scheme 4. Substrate scope of the deoxygenative coupling of alcohols with fluorenones. Unless otherwise noted, the reaction was performed with the conditions: fluorenone 1 (1 mmol), alcohol 2 (2 mmol), Bu₄NCIO₄ (1 mmol), Bu₃Ni (0.15 mmol), graphite rod anode, lead plate cathode, constant current (20 mA), 5 hours (3.7 F/mol), CH₃CN (3 mL), EtOAc (7 mL), undivided cell, 50 °C.

Synthetic Utility

The synthetic utility of the electrochemical cross-coupling of alcohols and fluorenones was further demonstrated by large-scale (~20 g) reaction and derivatization of product 3a and 4a (Scheme 4). With simple modification of reaction conditions, the electrochemical cross-coupling reactions were readily scaled up to 100 mmol, thereby delivering the expected diol 3a (84% yield, 24.2 g) and tertiary alcohol 4a (55% yield, 14.9 g). To our delight, the multi-gram-scale reaction exhibited higher current efficiency (2.3 F/mol, 3.5 F/mol) when compared to the identical small-scale reaction (4.7 F/mol, 3.7 F/mol), even at lower catalyst loading (10 mol%,
7.5 mol%). These features make the electrochemical protocol appealing in practical application. To demonstrate the versatility of products, several transformations, including dehydration, ring expansion, Friedel-Crafts alkylation and azidation were investigated. With catalysis of proton acid (TsOH) and Lewis acid (Sc(OTf)₃), dehydration of 3a and 4a proceeded smoothly to give product 5 and 6, respectively. Ring expansion of the 9H-fluoren-9-ol can be readily achieved through pinacol-rearrangement and migration of tertiary azides, thereby giving corresponding phenanthrol (7) and phenanthridines (8, 9). Moreover, Friedel-Crafts alkylation between 9H-fluoren-9-ols and triphenylamine were explored to access organic luminophores. To our delight, dialkylated and trialkylated product 10 and 11 were selectively produced. Both products showed excellent fluorescence properties in solid state with maximum emission wavelength at 412 nm and 407 nm, which could serve as potential candidates for applications in blue electrophosphorescent devices. Additionally, azidation of 9H-fluoren-9-ols were further studied and corresponding azide products (12, 13) were observed with nearly quantitative yields. Specifically, selective azidation of diol (3a) gives an α-azido alcohol 12, and it could transform into α-amino alcohol via a facile hydrogenation.
Scheme 5. Decagram scale reaction, and derivatization of products

**Mechanism Study**

To better understand the reaction mechanism, we performed the electrolysis in a divided cell (Eq. a, Scheme 6). Both the reactions were completely shut down, illustrating that both the anodic oxidation and the cathodic reduction are essential for the electrochemical transformations. Radical scavenger (1,1-diphenylethylene) was also employed in the reaction (Eq. b, Scheme 6). It was found that both products 3a and 4a were still formed, albeit with decreased yields. This result suggested that the electrochemical transformations potentially involved multiple pathways. To gain further insights into the reaction pathways, a series of control experiments were conducted. Firstly, a KIE study (Eq. c, Scheme 6) showed that cleavage of benzylic C-H is not the rate-determining step in the direct coupling reaction. Secondly, the optically pure substrate (R-1-phenylethanol)
furnished the racemic product, hinting that the possibility that an $S_n1$ or radical pathway may be operative in the deoxygenative coupling reaction (Eq. d, Scheme 6). Thirdly, the reactions of benzaldehyde (14) and benzyl iodide (15), as proposed intermediates in the reaction, were investigated to react with 9-fluorenone. The corresponding products were detected but in dramatically decreased yields (Eq. e and f, Scheme 6). Specifically, direct reductive coupling between benzyl halides (iodide, bromide, chloride) and 9-fluorenone resulted in only trace amount of product. Furthermore, using portion-wise addition of benzyl iodide was observed to improve the reaction performance. Taken together, these observations indicated that a reductive radical-coupling pathway is unlikely to be the main route in either of the electrochemical transformations.

Scheme 6. Control experiments

Next, a cyclic voltammetry study was conducted. As shown in Figure 2a and 2b, both TEMPOL and $^n$Bu$_4$NI are more susceptible to oxidation when compared to the corresponding substrates. Treatment of TEMPOL and $^n$Bu$_4$NI with excessive amounts of benzyl alcohol and triphenylphosphine, respectively, led to a noticeable
increase of the oxidative peak arising from these catalysts (Figure S8-S9). This demonstrated the catalytic role of TEMPOL and $^6$Bu$_4$NI in the anodic oxidation reaction. The cathodic behavior of substrates was also explored with cyclic voltammetry, and it showed that 9-fluorenone is the cathodically active substrate (Figure 2c, 2d) in the both reactions with a less negative potential, in comparison to either of the intermediate benzaldehyde (Figure S12) or benzyl iodide (Figure S13).

**Figure 2.** Cyclic voltammograms of substrates and catalyst, using a glassy carbon working electrode and Pt wire and Ag/AgNO$_3$ (0.1 M in CH$_3$CN) as counter and reference electrodes at a 100 mV·s$^{-1}$ scan rate. a. Anodic
behavior in the direct coupling reaction; b. Anodic behavior in the deoxygenative coupling reaction; c. Cathodic behavior in the direct coupling reaction; d. Cathodic behavior in the deoxygenative coupling reaction.

Based on these observations and prior literature reports, plausible mechanisms are proposed for both the direct coupling (Figure 3a) and deoxygenative coupling reaction (Figure 3b). Two possible intermediates radical anion (16) and dianion (17) could be generated in the reaction, which might lead to multiple reaction pathways. Due to aromaticity, dianion 17 might be the major reactive species. In the direct coupling reaction, inner-sphere electron transfer between TEMPOL+ and benzyl alcohol gives intermediate benzaldehyde 14 (Figure 3a). The low concentration of benzaldehyde makes it available to proceed via a nucleophilic addition with dianion 17 to give species 18, which undergoes a further protonation to give the direct coupling product 3a. Alternatively, the in-situ generated benzaldehyde may diffuse to the surface of the cathode where it is reduced to anion radical 19, which undergoes radical coupling with 16 and protonation to afford diol 3a. For the deoxygenative coupling reaction, anodic oxidation facilitates the deoxygenative iodination of alcohol to deliver benzyl iodide 15 (Figure 3b). The slowly released intermediate can be intercepted by 17 through an S_N1 pathway. The resulting radical species 20 proceeds via protonation to give product 4a. Pathways involving reductive radical coupling between 21 and 16 are regarded as another plausible reaction route.

**Figure 3.** Proposed reaction mechanism for the cross-coupling reaction.
Conclusion

In conclusion, we develop a paired electrolysis strategy for the cross-coupling of alcohols with fluorenones, which is compatible with both direct coupling and deoxygenative coupling reaction. With the two catalytic systems, broad range of non-symmetric 1,2-diols (89 examples) and tertiary alcohols (67 examples) are selectively accessed. The power of the electrochemical transformations is demonstrated in the late-stage functionalization of natural products, and the versatile derivatization of products. The convergent paired electrolysis strategy may have significant implications for more coupling reactions.

Supporting Information

Supporting Information is available and includes experimental procedures, characterization data, NMR spectra, and single crystal data.

Conflict of Interest

There is no conflict of interest to report.

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References


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**Table of Contents Graphic (required)**

- **Direct coupling**: 89 examples >20 g scale
- **Deoxgenative coupling**: 67 examples >10 g scale
- • catalyst-dependent selectivity
good functional-group tolerance