Direct Hydroxylarylation of Benzylic Carbons (sp^3/sp^2/sp) via Radical-Radical Cross-Coupling Powered by Paired Electrolysis

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Abstract

Diaryl alcohol moieties are widespread in pharmaceuticals. Existing methods for the synthesis of diaryl alcohols require the use of pre-functionalized benzylic alcohols, aromatic aldehydes or ketones as starting materials. Herein, the first convergent paired electrochemical approach to the direct hydroxylarylation of unactivated benzylic carbons (sp^3/sp^2/sp) is declared. This protocol features direct functionalization of unactivated benzylic C(sp^3)–H bonds and benzylic sp^2/sp-carbons, mild conditions (open air, room temperature), environmentally friendly procedure (without any external catalyst/mediator/additive), and direct access to sterically hindered alcohols from inexpensive and readily available alkyl/alkenyl/alkynylbenzenes. Mechanistic studies, including divided-cell experiments, isotope labeling, radical trapping, electron paramagnetic resonance (EPR), reaction kinetics, and cyclic voltammetry, strongly support the proposed radical-radical cross-coupling between transient ketyl radicals and persistent radical anions. Gram-scale synthesis and diversification of drug derivative have visualized the tremendous potential of this protocol for practical applications.

Introduction

Water and alcohols are both substances containing hydroxyl group. The former is widely considered to be the origin of life; the latter has always been the most important synthetic block in organic chemistry[1]. On top of that, the hydroxyl group is also one of the most important functional groups in the structure of marketed drugs. According to the ChEMBL data set, 37% of clinically approved drugs contain at least one hydroxyl group[2]. Among these drugs, diaryl alcohols are commonly encountered fragments (Fig. 1).

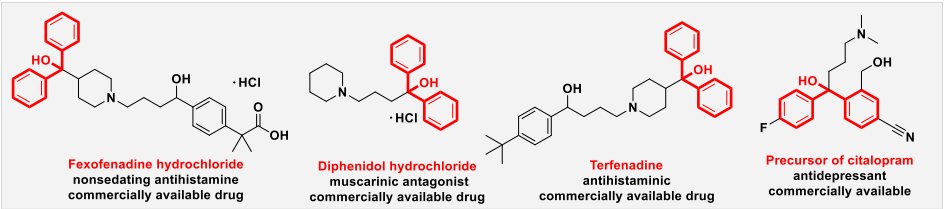
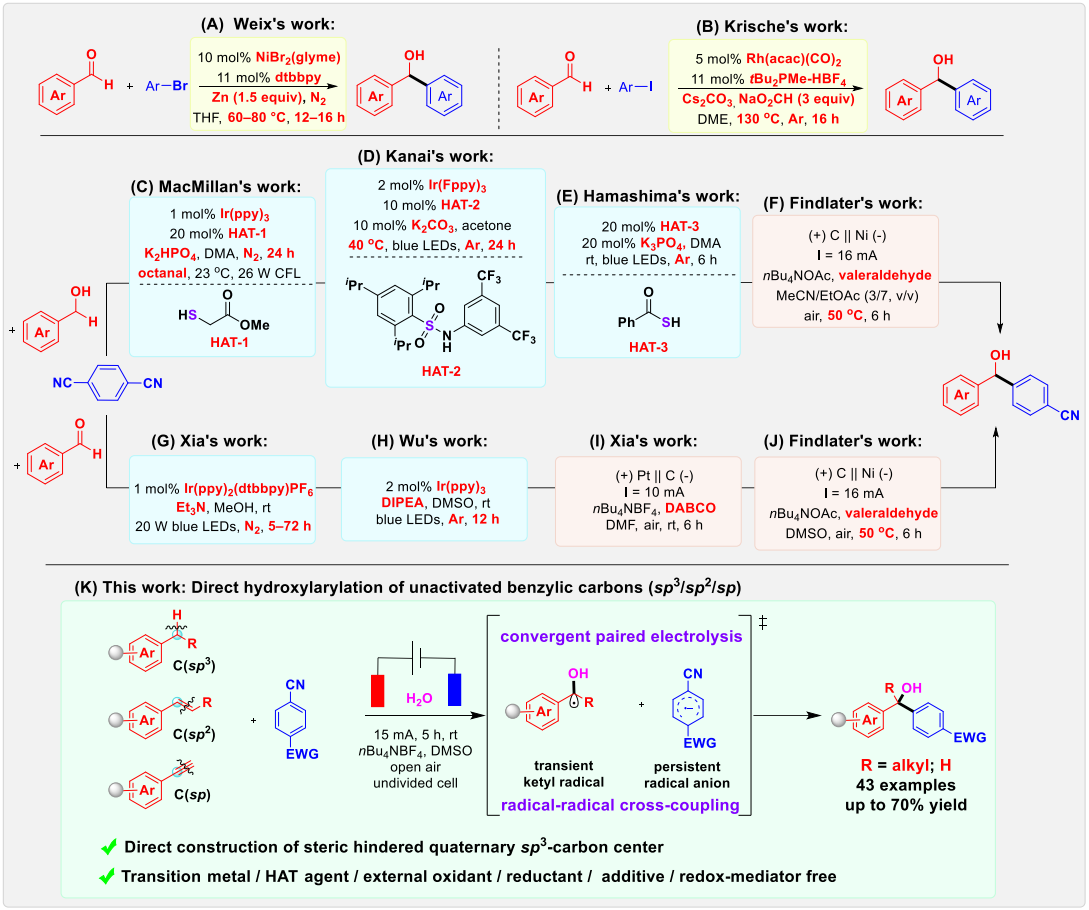


Fig. 1 The ubiquitous diaryl alcohol skeleton in medicine chemistry

As early as more than one century ago, chemists began to use Barbier or Grignard reaction[3] to prepare alcohols from aryl halides. However, the applicability of such reactions is limited due to the strictly anhydrous and anaerobic Schlenk technique required for the high reactivity of organometallic reagents. Lately, the reductive coupling of aryl halides and aromatic aldehydes (or ketones) catalyzed by transition metals has emerged as an alternative strategy for Grignard reaction, such as nickel catalysis reported by Weix[4] (Scheme 1A) and rhodium catalysis reported by Krische[5] (Scheme 1B). However, these methods require additional equivalents of reductants and high temperatures. During our further explorations with benzylic arylations, we were inspired by a series of seminal reports on photo- and electrochemical processes involving 1,4-dicyanobenzene (1,4-DCB). For example, in 2013, MacMillan's group[6] reported the direct arylation of benzylic alcohol via Ir photocatalysis and thiol as a hydrogen atom transfer (HAT) agent (Scheme 1C). Similar to this pioneering work, Kanai[7] and Hamashima[8] successively performed similar reactions using different HAT agents (Scheme 1D & 1E). Xia[9] and Wu[10] independently employed the reductive single electron transfer (SET) strategy (Scheme 1G & 1H) to achieve the radical-involved benzyl arylation from aromatic aldehydes and 1,4-DCB. In contrast to photochemistry, where the aforementioned inspiring works are blooming, such benzylic transformations are rarely well studied in organic electrochemistry. Recently, Xia[11] continued with his previous method of reductive coupling in an electrochemical manner (Scheme 1I). Findlater[12] obtained benzyl arylation products by electrochemical methods from benzylic alcohols and aromatic aldehydes, respectively (Scheme 1F & 1J), which required valeraldehyde as an additive at elevated temperature.

Collectively, the aforementioned photochemical benzylic arylations required the participation of photocatalysts[6,7] or HAT agents[8], inert gas protection, base as an additive, and time-consuming conditions. With regards to electrochemical reactions, sacrificial mediators[11] or additives[12] were necessary. Most importantly, the starting materials for both means are pre-functionalized alcohols or aldehydes. Thus, we believe this benzylic transformation has the potential for further optimization.



Scheme 1. Previously reported benzylic arylation procedures (A–J) and this work (K)

The direct C–H activation[13], which is well-known due to the characteristics of atom economy and step economy[14], can significantly reduce the generation of waste and avoid the pre-functionalization of the substrates. Consequently, this kind of powerful chemical transformation has been extensively applied to the construction of C–C[15], C–N[16], C–O[17] and C–F bonds[18], as well as other conversions[19]. The benzylic C(sp^3)–H is one of the most typical C–H bonds and exists in abundant chemicals, which is also present in many biologically active compounds[20], and nearly 25% of the 200 best-selling drugs contain this structural moiety[21]. Lately, the electrochemical benzylic C(sp^3)–H activation has been widely used for C–N[22] or C–O[23] coupling. However, to the best of our knowledge, the concurrent formation of C–C and C–O bond within one step through unactivated benzylic C(sp^3)–H functionalization has rarely been reported.

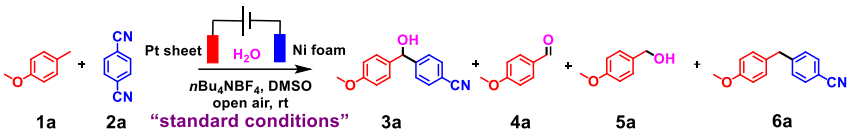
Currently, the reported paired electrolysis reactions are dramatically increasing, and traditionally they are mainly divided into three categories: parallel, sequential, and convergent paired electrolysis[24]. In this context, we intended to make full utilization of the convergent paired electrolysis and the radical philicity[25] to realize the direct hydroxylarylation of unactivated benzylic C(sp^3)–H without any external redox mediator. According to the previous literature[22,23], we had noticed that it is feasible to oxidize the benzylic C(sp^3)–H to benzylic C–radical under anodic oxidation, but this unstable intermediate can easily be further oxidized to benzyl carbocation[26]. Hence, we speculated as follows: the carbocation is nucleophilically attacked by water to form the corresponding benzylic alcohol, which is then further oxidized at the anode to generate the ketyl radical[27]. And at the counter electrode, the well-studied classic radical precursor 1,4-DCB[28] generates the persistent radical anion via reductive SET. Finally, radical intermediates

formed at the anode and cathode undergo radical-radical cross-coupling. Guided by this logic, the chemoselective synthesis of high value-added sterically hindered diaryl alcohols from inexpensive alkylbenzenes may come true. Herein, a new method for direct hydroxylarylation of unactivated benzylic C(sp^3)–H bonds is declared, which is also applicable to direct hydroxylarylation of benzylic sp^2/sp-carbons (Scheme 1K).

Results and discussion

Evaluation of the proposed strategy was first performed using 4-methylanisole (**1a**) and 1,4-dicyanobenzene (**2a**) as model substrates at room temperature (rt). After the systematic screening of various reaction parameters, optimal conditions were determined as: using dimethyl sulfoxide (DMSO) as the solvent, nBu$_4$NBF$_4$ as the electrolyte in an undivided cell equipped with Pt sheet anode and Ni foam cathode under a constant current of 15 mA (Table 1, entry 1). Electric current proved to be essential for this reaction to occur (Table 1, entry 2), and changing the electrolyte can also affect the yield of the reaction (Table 1, entry 3). More importantly, the choice of nickel foam as the cathode is critical to the chemical selectivity of the reaction (Table 1, entry 6), otherwise more by-products would be generated, such as benzylic alcohol **5a** derived from the anodic oxidation of **1a**, **4a** generated from the further oxidation of **5a**, and the arylated by-product **6a** (Table 1, entries 4 & 5). The yield of the hydroxyarylated product **3a** decreased accordingly when the current was reduced (Table 1, entry 7), the temperature was raised (Table 1, entry 8), or the amount of water was reduced (Table 1, entry 9). For detailed condition optimization, please see the Supporting Information (SI), Section 3 (§3), Tables S1–S5. And during the process of optimization, three additional by-products were isolated, see details in SI, §8.

Table 1. Control experiments



Entry	Deviation from standard conditions[a]	Conversion (%)[b]		Yield (%)[b]			
		1a	**2a**	**3a**[c]	**4a**[d]	**5a**[d]	**6a**[c]
1[e]	none	73	96	62	1	8	8
2	w/o current	0	0	0	0	0	0
3	*n*Bu$_4$NOAc	60	93	30	1	3	4
4	(+) C plate // Pt sheet (-)	69	95	20	3	12	19
5	(+) C plate // C plate (-)	67	98	10	4	12	19
6	(+) C plate // Ni foam (-)	72	92	57	1	7	8
7	10 mA, 7.5 h	74	98	31	3	5	13
8	50 °C	70	98	41	3	6	6
9	5 equiv H_2O	70	93	57	1	9	5

[a] Standard conditions: **1a** (1.0 mmol, 2 equiv), **2a** (0.5 mmol, 1 equiv), *n*Bu$_4$NBF$_4$ (0.1 mmol, 0.2 equiv), H_2O (5.0 mmol, 10 equiv), DMSO (5 mL), Pt sheet anode, Ni foam cathode, constant current = 15 mA, 5 h, rt, open air, undivided cell, reactions performed using Standard ElectraSyn 2.0 vessel (10 mL). [b] The yields and conversions were determined by ^{1}H NMR using dimethyl terephthalate as the internal standard. [c] Yield based on limiting reagent **2a**. [d] Yield based on excess substrate **1a**. [e] The experiment was repeated three times, and the average value was taken as shown.

With the optimized reaction conditions in hand, our attention was then focused on evaluating the generality of the reaction with 1,4-DCB and more diverse alkylbenzenes. As shown in Fig 2, alkoxy substituted methylbenzenes, such as *p*-ethoxy and *p*-cyclopentyloxy substituted methylbenzenes, smoothly gave corresponding products (**3b** and **3c**) in higher yields than the model substrate (**3a**). 3,4,5-Trimethoxytoluene also resulted in a satisfactory yield (**3d**). In addition, 1-methoxy-2,4-dimethylbenzene (**1e**) was selectively functionalized at the 4-methyl group, showing good regioselectivity, which may be due to the dual effects of electronic density and steric hindrance. For 1-methoxy-2-methylbenzene (**1f**), the reaction could overcome steric hindrance and gave the desired product **3f** in a relatively low yield. Changing the alkoxy group to the less electron-donating phenoxy group led to a much lower yield (**3g**). Similarly, switching to electron-neutral phenyl group resulted in a moderate yield (**3h**). Note that substrates with an electron-withdrawing group (EWG) were difficult to undergo benzylic C–H oxidation in previous reports[22,23] and we were satisfied to find that even EWG substituted **1i** could afford the corresponding product **3i**, albeit in a much lower yield. 4-*tert*-Butyltoluene could also smoothly participate in the reaction, providing the corresponding product **3j**.

With the above successful examples, we extended the substrate scope to the construction of quaternary sp^3-carbon centers. Consistent with previous rules, electronic effects still played a crucial role. Substrates with strong electron-donating alkoxy groups (**3k**–**3p**) gave higher yields than those with weak electron-donating or electron neutral groups (**3q**–**3t**). Intriguingly, *p*-methoxy phenylpropanol and *p*-methoxy phenylbutanol reacted selectively at the benzylic position, providing the target products in high yields, respectively (**3n** and **3o**), while the primary alcohol moiety remained intact. Ester group was also tolerated in this transformation to afford the corresponding product (**3p**) in a satisfactory yield. Both 4,4'-diethyl-1,1'-biphenyl and 1,3,5-triethylbenzene reacted only at one of the benzylic C(sp^3)–H bonds (**3r** and **3t**). Finally, we found that the corresponding transformation could also occur at the benzylic position of heteroaryl compound (**3u**), although the yield was lower.

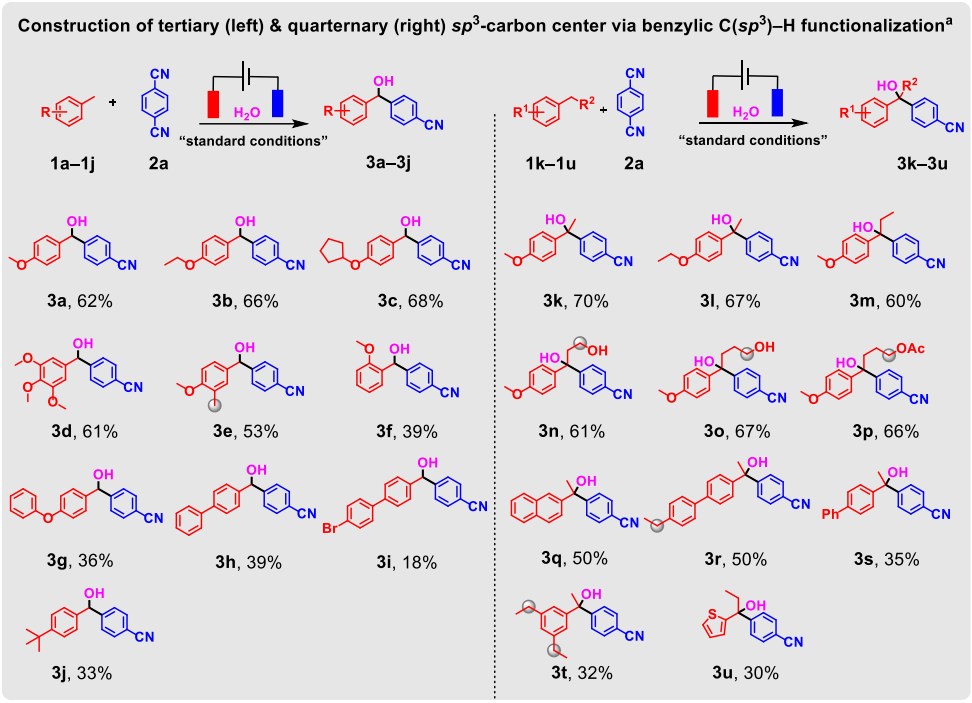


Fig 2. Scope of benzylic C(sp^3)–H bonds. [a] Isolated yields, and the reactions were carried out under standard conditions in the scale of 0.5 mmol with **2a** as the limiting reagent.

In the subsequent studies, we serendipitously found that the established methodology of hydroxylarylation of benzylic C(sp^3)–H could be directly used in the functionalization of benzylic carbon (sp^2/sp), which indicated the excellent applicability of this method. The alkenylbenzenes (**1v**–**1z**) and alkynylbenzenes (**1aa**–**1ab**) could also generate the desired hydroxyarylated products under the same standard conditions (Fig. 3A). It is worth mentioning that in the presence of benzylic C(sp^3)–H, the reaction selectively occurred at the site of benzylic sp^2-carbon (**1y**) or sp-carbon (**1ab**), showing good chemoselectivity. Note that for alkenes, the hydroxylarylation involved C=C double bond cleavage. More absorbingly, some unpredictable products were isolated during the whole process of substrate expansion (Fig. 3B), and the possible pathways of related transformations were shown in SI, §9, Fig. S24. In addition to the above results, one of the cyano groups in 1,4-DCB was successfully replaced with other electron-withdrawing groups, which further broadened the application scope of the reaction (Fig. 3C).

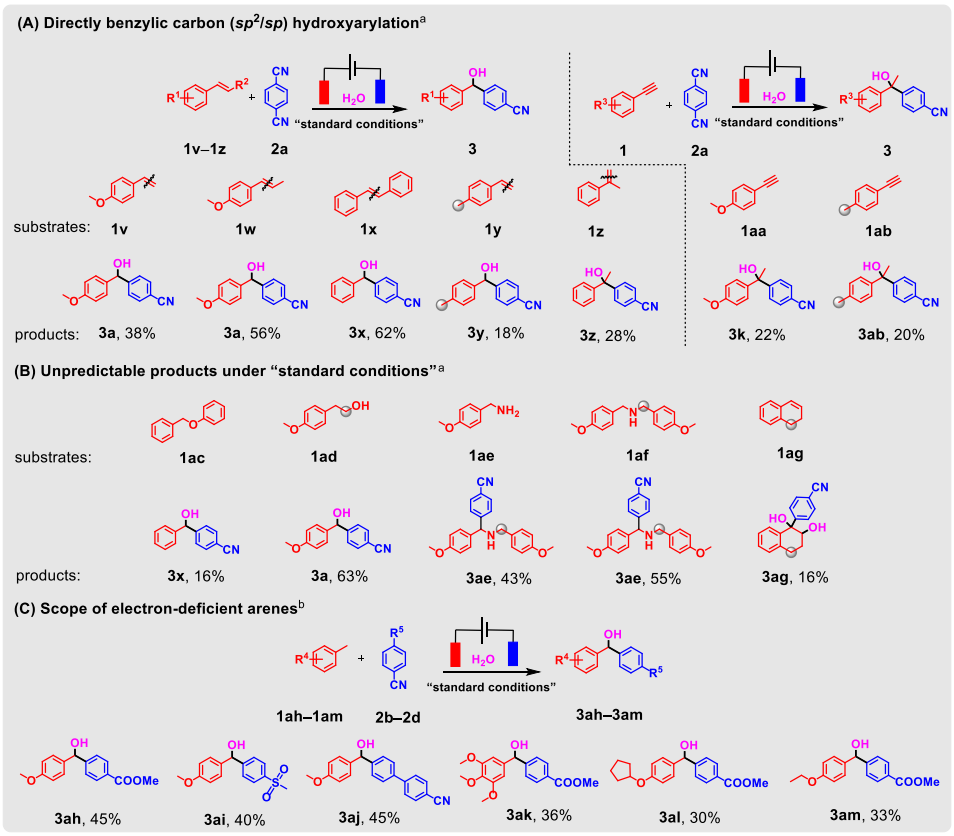


Fig 3. Scope of benzylic carbon (sp^2/sp) and alternatives of 1,4-DCB. [a] Isolated yields, and the reactions were carried out under standard conditions in the scale of 0.5 mmol with **2a** as the limiting reagent. [b] **2a** was replaced with the following substrates: **2b** (4-cyanobenzoic acid methyl ester), **2c** (4-(methylsulfonyl)benzonitrile), **2d** (4,4'-biphenyldicarbonitrile).

As known, the structural modifications of bioactive compounds are crucial to pharmaceutical development. Even minor structural changes may alter the activity of drug candidates[29]. The reported methodology could be used for the selective functionalization of the ibuprofen derivative on the less sterically hindered benzylic C(sp^3)–H bond, showing its ability to diversify drug derivatives (Fig. 4A). To further illustrate the potential practicability of this method, the original experiment was scaled up to 20-fold (from 0.5 mmol to 10 mmol) (Fig. 4B), and the 50% isolated yield manifested the practical applicability of the method.

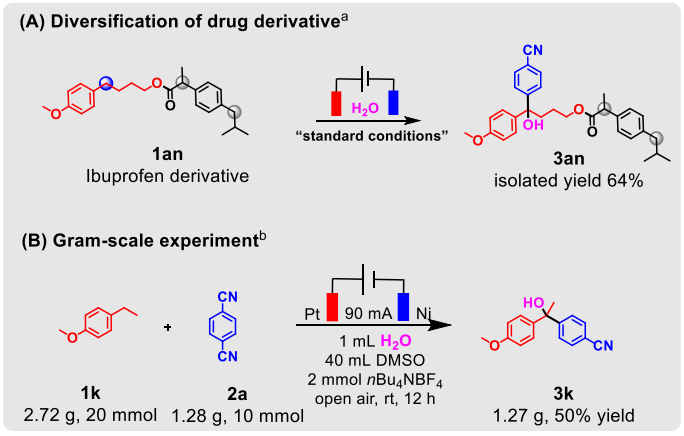


Fig 4. Potential applications of the reaction. [a] The reaction was carried out under standard conditions in the scale of 0.5 mmol with **2a** as the limiting reagent. [b] See reaction details in SI, §6.

Mechanism study

Control experiments were carried out to clarify the reaction mechanism of the benzylic C(sp^3)–H hydroxylarylation (Fig. 5). Firstly, we tried to initiate this reaction with traditional chemical oxidants, but the results showed that electric current is irreplaceable in this chemical transformation (Fig. 5A). Subsequently, the reaction was performed with a sacrificial anode, and as expected, no target product was detected. And when Ni foam was used as a sacrificial anode, the by-product 4,4'-biphenyldicarbonitrile (**2d**) (see structure in Fig. 7 and details in SI, §8, Fig. S19) derived from 1,4-DCB self-coupling was isolated (Fig. 5B), which illustrated that the anodic oxidation is required for this reaction, and 1,4-DCB can indeed be reduced at the cathode. Paired electrolysis placed a high demand on the efficient delivery of reactants between the anode and cathode. Therefore, without stirring, the delivery of reactants can only rely on static diffusion, making it difficult for the active intermediates generated from anode and cathode to collide effectively. Without stirring under standard conditions, the yield of the model reaction dropped sharply to 4%, suggesting that the reaction may be a paired electrolysis. Further, there was no target hydroxyarylated product formation when the experiment was carried out in a divided cell, demonstrating that the desired transformation is a paired electrochemical reaction (Fig. 5B). In addition, **5a** could react with 1,4-DCB to produce the target product **3a**, suggesting that **5a** may be the key intermediate in the reaction. This speculation was further supported by the reaction kinetics experiments (SI, §7.6, Fig. S10).

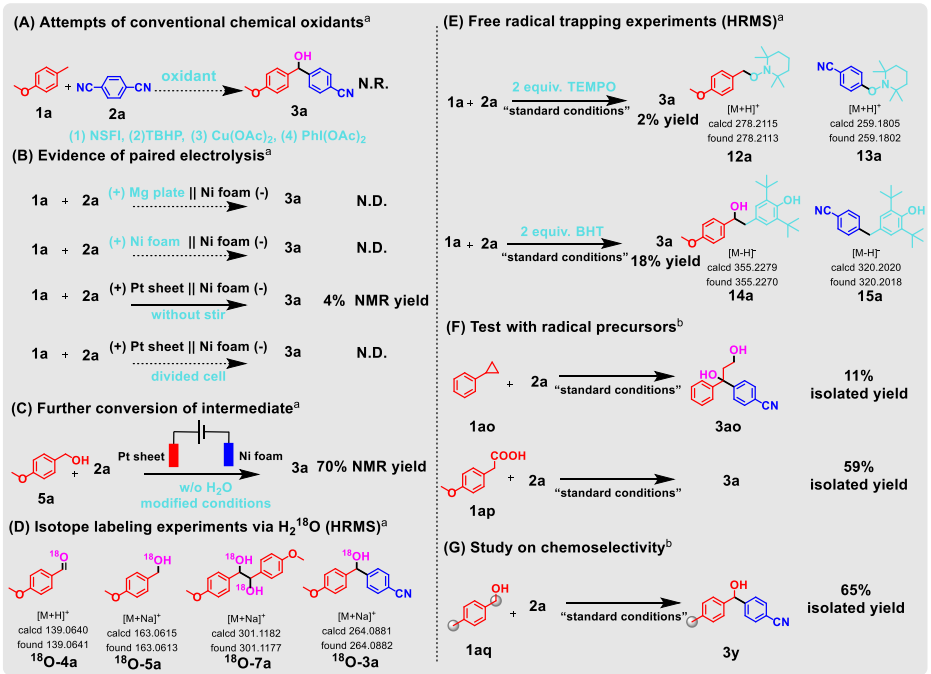


Fig 5. Studies on the mechanism of paired electrochemical process and evidence of radical-involved process. [a] See reaction details in SI §7. [b] Reactions were carried out under standard conditions in the scale of 0.5 mmol with **2a** as the limiting reagent.

Next, the isotope labeling experiments were carried out and existence of **^{18}O-3a** proved that the hydroxyl group in the product came from water, and the presence of **^{18}O-4a**, **^{18}O-5a** and **^{18}O-7a** provided further evidence for this conclusion (Fig. 5D). The yield decreased substantially with the addition of radical scavenger, 2,2,6,6-tetramethylpiperidinooxy (TEMPO) or butylated hydroxytoluene (BHT). The existence of **12a** and **14a** proved the formation of benzylic radical and

ketyl radical, and **13a** and **15a** further proved the generation of arene radical species (Fig. 5E). The transformation of radical precursors **1ao** to **3ao**, as well as **1ap** to **3a**, further illustrated that the reported hydroxylarylation involves a radical process (Fig. 5F). Additionally, the formation of **3y** exclusively from direct functionalization at the benzyl alcohol site in **1aq** further supported the hypothesis that once the benzylic alcohol is generated, it is much easier to react with 1,4-DCB (Fig. 5G).

To get a deeper insight into the mechanism, electron paramagnetic resonance (EPR) experiments were performed (Fig. 6A–C). Apparently, three completely different signals were detected when related compounds were separately treated with 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) under electrochemical conditions. The observed g-factors (SI, §7.3, Fig. S5–S9) for the spin adducts were very close to 2.0023 for free electrons[30], which provided more conclusive evidence for the proposed free radical mechanism.

More details about the mechanism were uncovered by the cyclic voltammetry experiments (SI, §7.7, Fig. S11–S18). As shown in Fig. 6D, an oxidation peak of **1a** in MeCN was detected at 1.74 V vs Ag/AgCl, which implied starting material **1a** is preferentially oxidized at the anode. The by-product benzylic alcohol **5a** (1.79 V vs Ag/AgCl) has an oxidation potential very close to **1a** and an extremely high current response[31], repeatedly showing that it may be the key intermediate in the reaction. These two rather close oxidation potentials were the key to the success of the proposed process. As for **2a**, there was no obvious oxidation peak in the test range, while its reduction potential (-1.64 V vs Ag/AgCl) further supported the paired electrochemical strategy (SI, §7.7, Fig. S15).

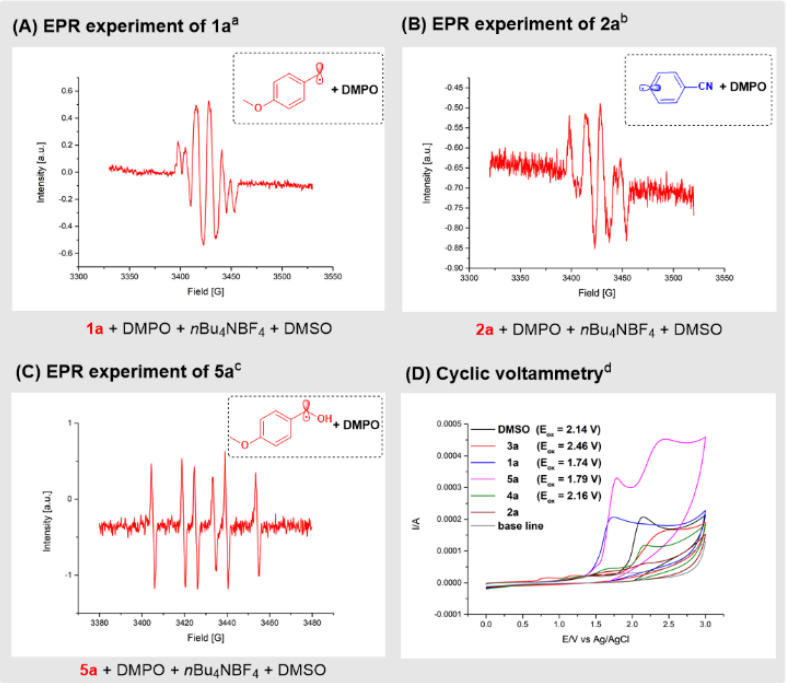


Fig 6. Electron paramagnetic resonance and cyclic voltammetry experiments. [a] EPR of **1a**-DMPO spin adduct, g-factor 2.00674. [b] EPR of **2a**-DMPO spin adduct, g-factor 2.00657. [c] EPR of **5a**-DMPO spin adduct, g-factor 2.00781. [d] The experiments were carried out with 0.01 M related compounds and 0.1 M nBu$_4$NBF$_4$ in MeCN, using glass carbon as working electrode, Pt wire as counter electrode, and Ag/AgCl as reference electrode at 100 mV/s scan rate.

Based on the above experimental results and literature reports[12], a plausible mechanistic explanation was proposed in Fig 7. Substrate **1a** is oxidized to an aryl radical cation via a SET

process and subsequently loses a proton to give benzyl radical **I**. The benzyl radical **I** undergoes further oxidation to the benzyl cation, which is then nucleophilically attacked by water to generate the benzyl alcohol **5a**[32]. As shown in Fig 6D, **5a** has an oxidation potential close to that of **1a**, so it can undoubtedly be oxidized like **1a** to form the more stable transient ketyl radical **II**[12]. At the counter part, **2a** can get one electron from the cathode to generate its radical anion, which as a persistent radical can preferentially react with ketyl radical **II** to yield the target product **3a**. As for the possible mechanism of benzylic carbon (sp^2/sp) functionalization, please see details in SI, §9, Fig. S20–S23.

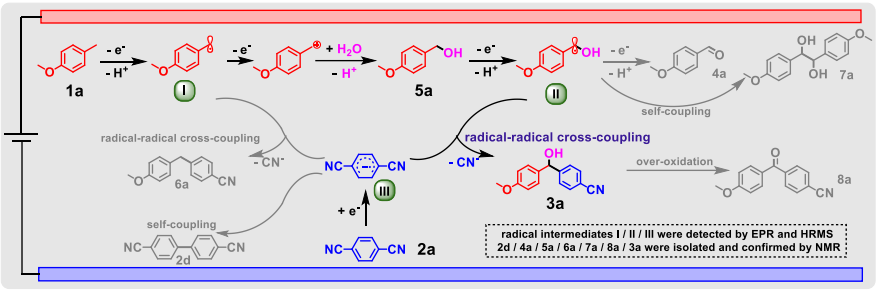


Fig 7. Proposed mechanism for the direct hydroxylarylation of benzylic C(sp^3)–H bond

Conclusion

Collectively, we have demonstrated the first convergent paired electrochemical approach to the direct hydroxylarylation of unactivated benzylic carbons (sp^3/sp^2/sp). The key step of the reaction is the formation of ketyl radicals generated from oxidation of benzylic alcohols (derived from direct functionalization of C(sp^3)–H bonds) or the reduction of phenyl aldehydes/ketones (obtained from direct activation of benzylic sp^2/sp-carbon). This versatile protocol, featuring excellent site selectivity, broad functional group compatibility, and easy scale-up, provides a convenient approach for the construction of sterically hindered alcohols, as well as the diversification of compounds containing drug structures. In addition, the mechanistic investigations showed that the reaction only occurs at the benzyl position, and this excellent chemical selectivity stems from the inherent properties of free radicals. Notably, the proposed strategy was strongly supported by the isolated by-products and mechanistic experiments. Given the operational simplicity and mild conditions, we believe that this green, economical protocol will attract more attention and obtain extensive applications in the field of organic synthesis.

Author Contributions

X.-W.W. developed the conditions and performed the experiements. R.-X.L., and Y.D. prepared the substrates. C.-S.H. analyzed the results. Z.G. and Y.-H.H. provided insightful suggestions in analyzing the data and editing the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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