CHEMISTRY

Electrochemical oxidation-induced etherification via C(sp³)—H/O—H cross-coupling

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Direct electrochemical construction of C—O bonds through C(sp³)—H functionalization still remains fundamentally challenging. Here, electrochemical oxidation-induced benzylic and allylic C(sp³)—H etherification has been developed. This protocol not only offers a practical strategy for the construction of C—O bonds using nonsolvent amounts of alcohols but also allows direct electrochemical benzylic and allylic C(sp³)—H functionalization in the absence of transition metal catalysis. A series of alcohols and benzylic and allylic C(sp³)—H compounds were compatible with this transformation. Mechanistically, the generation of aryl radical cation intermediates is the key to this C(sp³)—H etherification, as evidenced by radical probe substrate (cyclopropane ring opening) and electron paramagnetic resonance experiments.

INTRODUCTION

Ethers are widely found in pharmaceuticals and medicinally relevant natural products and likewise serve as important intermediates in synthetic chemistry (1–4). Consequently, major efforts have been devoted toward the construction of ethers (Fig. 1). Traditionally, the Williamson reaction (5–7), using alcohols and electrophiles containing leaving groups as coupling partners, has been widely used in primary ether synthesis. Because of the potential competing β-H elimination, low yields of secondary and tertiary ethers were obtained by these methods. Besides, Williamson etherification suffers from undesired waste and multiple steps owing to the need of prefunctionalization of substrates. Subsequently, etherification reactions via cross-coupling of two alcohols have been disclosed (8–10). In this regard, the need for either high temperature or hazardous reagents leads to complicated operation. In addition, acid- or transition metal-catalyzed hydroalkoxylation of alkenes has emerged as a powerful strategy for C—O bond formation, which still maintains considerable room for improvement in functional group tolerance (11–15). Despite the above publications and other published ether synthesis methods (16–19), a simpler and straightforward synthetic strategy for C—O bond formation is fascinating yet elusive (20, 21).

Recently, electrochemical oxidative intermolecular C—H/X—H (X = N, S, O) cross-coupling with release of hydrogen has substantially expanded access to valuable organic molecules (22–37). Electricity, serving as an environmentally friendly alternative to sacrificial oxidants, drives the chemical transformation. Under metal-free electrochemical condition, radicals, radical cations, or cations can be generated through electron transfer on the surface of the anode. Then, the reactions between the generated intermediate and other active substrates enable access to the target molecules along with the release of hydrogen at to cathode, which provides a privileged platform for oxidative C—H/X—H cross-coupling without the use of sacrificial oxidants and toxic catalysts. However, highly reactive intermediates selective for intermolecular cross-couplings under electrochemical conditions are difficult to handle. To address the challenge of selective C—H/X—H cross-coupling, the solvent quantities of one of were substrates were necessary, as exemplified by construction of C(sp²)—O bond and C(sp³)—O bond (30, 33). As a consequence, the art for the electrochemical generation of ethers through intermolecular C(sp³)—H/O—H cross coupling is at the start-up stage.

The disparity of redox potential of reaction substrates offers a possibility of selective activation of substrates. We hypothesized that etherification through C(sp³)—H/O—H cross-coupling under electrochemical conditions can be achieved by using the disparity of redox potential of alcohols and C(sp³)—H compounds, such as benzyl or allyl C(sp³)—H compounds (Fig. 1). In the reaction system, aryl radical cations can be easily formed from C(sp³)—H compounds via single-electron transfer (SET) processes at the anode. Nucleophiles, such as various alcohols, would attack the reactive radical cation to deliver target molecule concomitant with the release of hydrogen gas at cathode through a SET process.

Here, we describe an electrochemical oxidant-free protocol for the benzylic and allylic C(sp³)—H bond etherification using non-solvent amounts of alcohols as the nucleophile in a simple undivided cell under constant-current conditions. A series of alcohols and benzylic and allylic C(sp³)—H compounds were compatible with this protocol under mild conditions, delivering corresponding products in satisfactory yields. Mechanistic studies demonstrated that this reaction involved a SET process. The formation and resonation of aryl radical cation intermediates are the key to this transformation, which was evidenced by probe substrate (cyclopropane ring opening) and electron paramagnetic resonance (EPR) experiments.
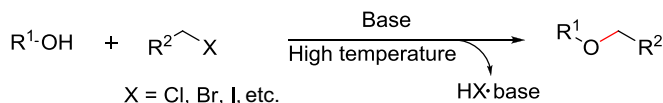
RESULTS AND DISCUSSION

Initially, indan (1a) and phenethyl alcohol (2a) were chosen as standard substrates. The desired product 3aa was obtained in 27% yield by using 10-mA constant current in an undivided cell. Pleasingly, 50% yield was delivered when we used Cs_2CO_3 as a base (table S1, entry 2). Moreover, after a screening of the electrode materials, a 56% yield of the desired product was obtained with the use of carbon as anode and nickel as cathode (table S1, entries 2 to 4). In addition, the desired product can be acquired in CH_3CN (table S1, entry 5). Further experiments have shown that the mixture of 1,2-dichloroethane (DCE) and Et_2O increased the yield to 60% (table S1, entry 7), and no obvious by-products were observed. Subsequently, the control

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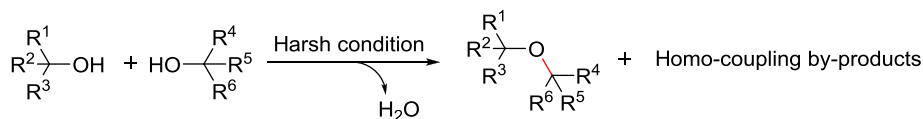*These authors contributed equally to this work.
†Corresponding author. Email: aiwenlei@whu.edu.cn

A Williamson ether synthesis

B Coupling between alcohols

C Addition of alkenes

Hypothesis: electrochemical oxidation–induced benzylic and allylic C(sp^3)–H activation

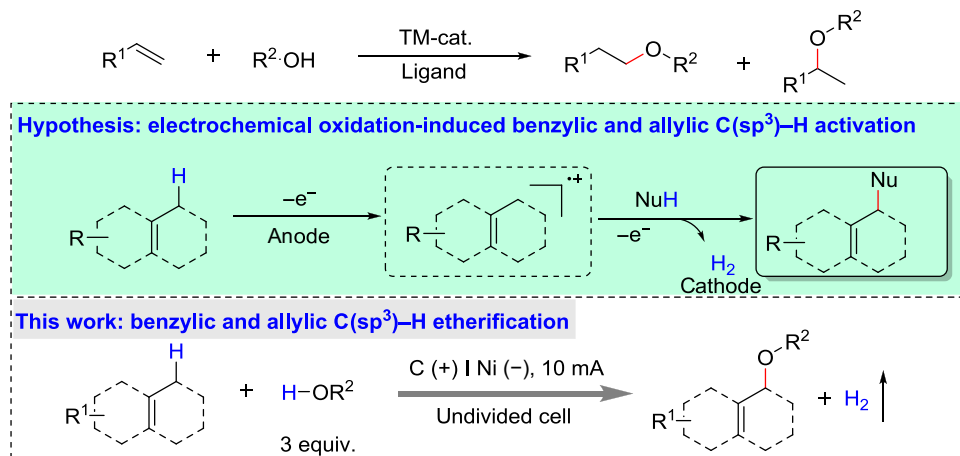**This work: benzylic and allylic C(sp^3)–H etherification**

Fig. 1. Previous etherification reactions and research scheme of this work.

experiments were also performed to evaluate the effect of the types of base. Cs_2CO_3 proved to be an optimal base for this C—H bond etherification (table S1, entries 10 and 11). Thereafter, the electrolytes were investigated. The yield decreased when $^nBu_4NClO_4$ was replaced with $^nBu_4NBF_4$ (table S1, entry 12). Furthermore, we could not further improve the reaction yield when we prolonged the reaction time, which might be because the product was decomposed with the extension of time. It is noteworthy that no reaction occurred without electricity (table S1, entry 14). Fifty percent yield of **3aa** was obtained in ambient atmosphere, demonstrating that the reaction is not sensitive to the air (table S1, entry 15).

With the optimized conditions, we evaluated the scope of this electrochemical C—O bond formation (Fig. 2). Alcohols with aryl groups were first tested (**3aa**-**3ak**). Position of substances on the aromatic ring had no obvious influence on the efficiency of this protocol. **3aa**-**3ag** can be obtained in considerable yield. Halides, such as F, Cl, and Br, which can be transformed into other molecule via coupling reactions, were well tolerated. Moreover, benzyl alcohol, being easily oxidized to benzaldehyde under oxidative conditions (*38*), was successfully transformed to corresponding products **3ah**. β-Methylphenethyl alcohol reacted smoothly with indan (**1a**) to deliver desired product (**3ak**) in 62% yield. Subsequently, other alkyl alcohols were evaluated (**3al**-**3az**). This transformation was also compatible with a series of cyclic alcohols, affording **3al**-**3ap** in satisfactory yields. Among them, adamantanol offered a lower yield of product because of the steric hindrance (**3al**). Similarly, other hin-

dered alcohols were also amenable to this C—O bond formation strategy with moderate yields (**3ar** and **3au**). Reductively labile groups, such as alkynes and vinyl, were amenable to this electrochemical strategy. **3ap** and **3aw** were accessed through C—O bond formation despite the nucleophilic sensitivity of alkyl chloride and cyclopropyl. Alcohols containing multiple F atom reacted smoothly with indan to deliver the desired products (**3ax**). Alcohols, serving as important structural motifs, have widespread application in medical treatments (*39*). Pharmaceutical molecules, which contain hydroxyl group such as menthol and epiandrosterone, were suitable coupling partners in this protocol, delivering corresponding products in satisfactory yields (**3ay** and **3az**). With respect to C(sp^3)—H compounds, different kinds of substrates were investigated (**3ba**-**3ja**). 1,2,3,4-Tetrahydronaphthalene was tolerated (**3ba**). Furthermore, **3ca** and **3da** were successfully obtained. Highly selective C—H bond etherification of ethyl groups was achieved rather than of methyl groups when we used 4-ethyltoluene to react with phenethyl alcohol (**3ea**). Similar result occurred with the use of 2-ethyl-5-methylthiophene as coupling partner (**3fa** and **3ga**), which also means that heterocyclic compounds were well tolerated in this etherification reaction. As is known, activation of allylic C—H bond remains a great challenge. In this work, allylic C—H etherification can be achieved, providing a practical way for the functionalization allylic C—H bond. Cyclohexene reacted smoothly with phenethyl alcohol and hex-3-yn-1-ol, forging **3ha** and **3ia** in 50 and 46%, respectively. To our delight, cyclododecene was also amenable to this electrochemical etherification reaction (**3ja**).
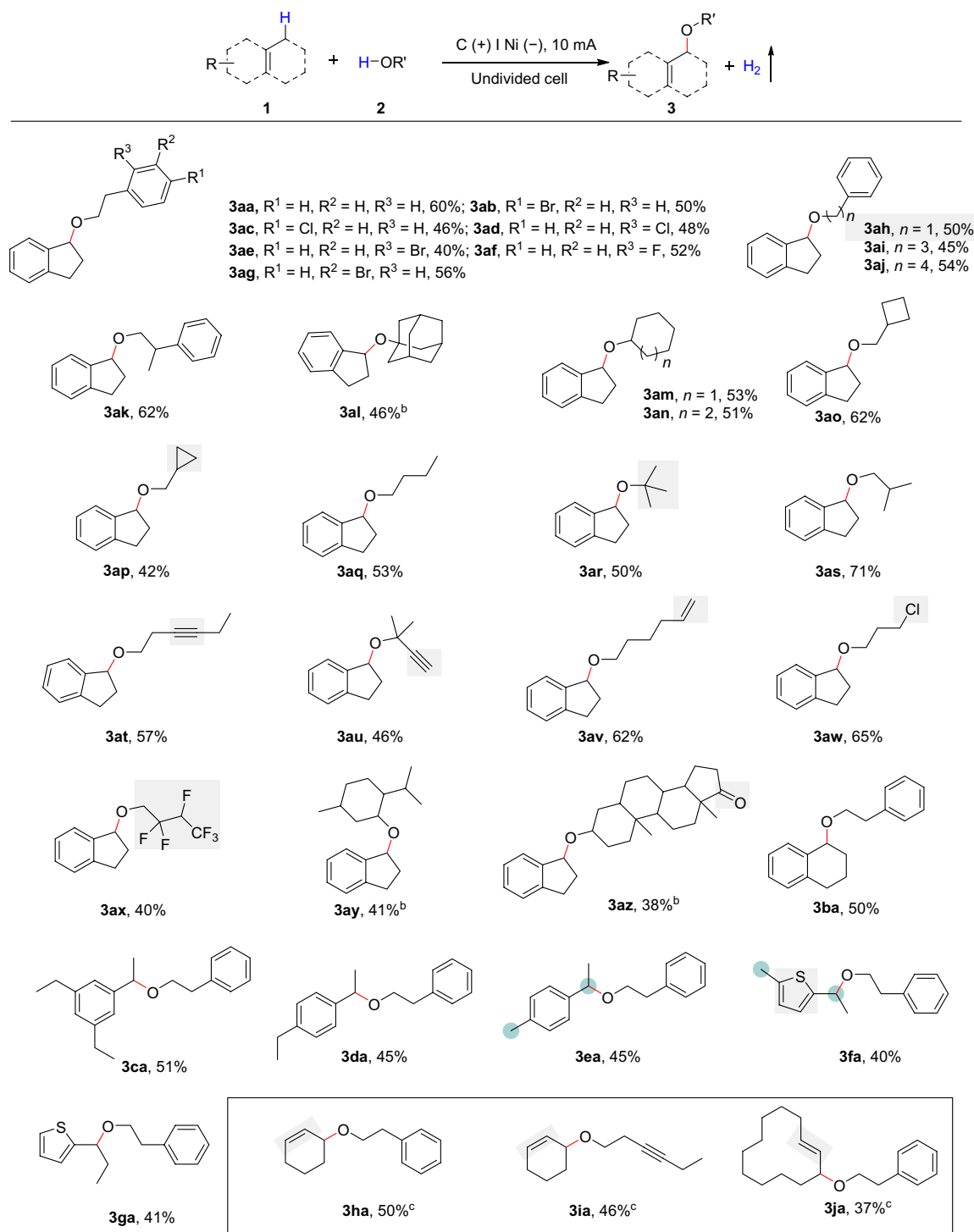
Fig. 2. Substrate scope for the electrochemical etherification. Standard conditions: Carbon rod anode, nickel plate (15 mm by 15 mm by 1 mm) cathode, constant current = 10 mA, **1** (0.5 mmol), **2** (3 equiv.), ^{n}Bu$_4$NClO$_4$ (0.5 equiv.), Cs$_2$CO$_3$ (2 equiv.), 20°C, in DCE/Et$_2$O (6/0.5 ml) under N$_2$ atmosphere for 3.5 hours, and an undivided cell. [b]DCE/DCM (4/2 ml). [c]Carbon rod anode, Pt plate (15 mm by 15 mm by 0.3 mm) cathode, in DCE (6 ml) under N$_2$ atmosphere for 3.5 hours, 12°C.

Subsequently, control experiments were conducted to know more detail about the mechanism of this electrochemical C—H bond reaction, as shown in Fig. 3. Radical clocks have been recognized as efficient tools for radical verification, providing an obvious ad-

vantage in experiment design. Cyclopropylbenzene was used as coupling partner, offering a ring-opened product (**3la**), revealing the existence of an aromatic carbon radical intermediate (Fig. 3A). In addition, 2,4-di-tert-butyl-4-methylphenol could react with **2a**,
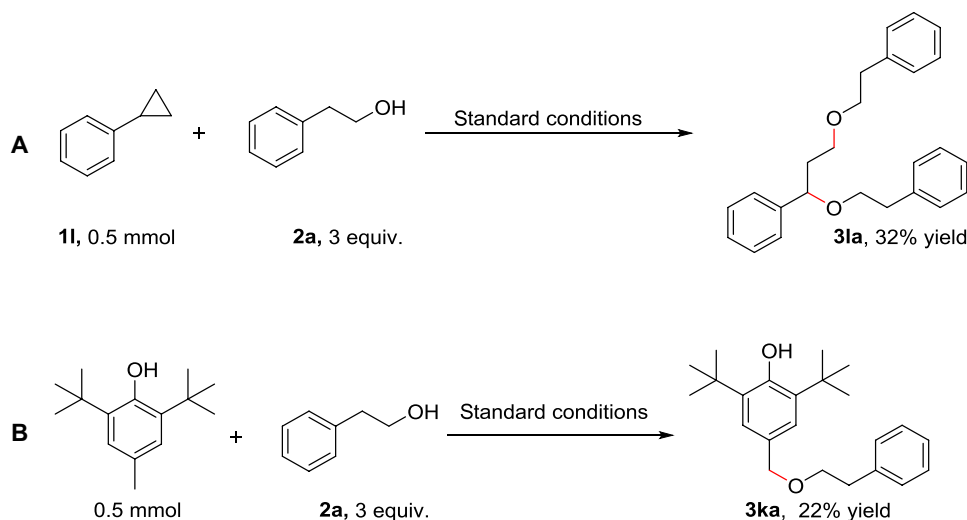
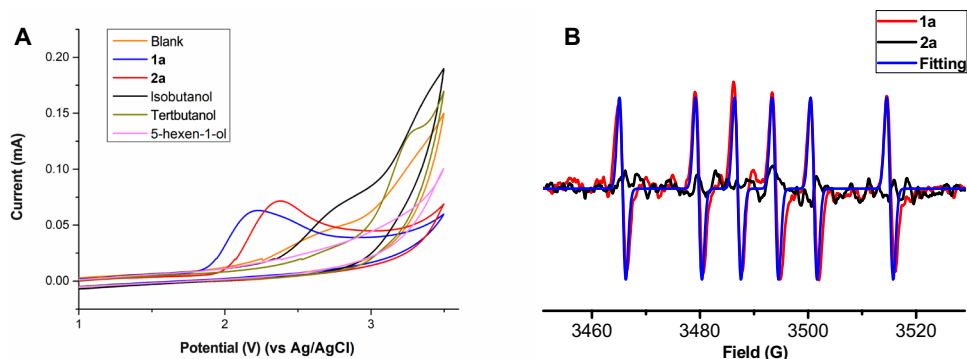**Fig. 3. Control experiments.** (**A**) Radical clock experiment. (**B**) Radical trapping experiment.

Fig. 4. Mechanistic studies. (**A**) Cyclic voltammograms of 0.01 M related compounds in 0.24 M $^{n}Bu_4NClO_4$ in DCE, using glass carbon working electrode, Pt wire as counter electrode, and Ag/AgCl as reference electrode at 50-mV/s scan rate. (**B**) EPR experiments.

delivering **3ka** (Fig. 3B). This result suggests that the mechanism in which the alcohol is oxidized to O-centered radical cannot be excluded in this transformation.

To get deeper insight into the mechanism, cyclic voltammetry was carried out to study the redox potential of **1a**, **2a**, and other alcohols, as shown in Fig. 4A. An oxidation peak of **1a** in DCE was detected at 2.22 V. Similarly, oxidation peaks of **2a** could also be observed about 2.38 V. On the other hand, other alkyl alcohols have much higher potential than phenethyl alcohol (**2a**). The results reveal that indan (**1a**) was more easily oxidized than most of the alkyl alcohols (Fig. 4A). In addition, the potential of **1a** and **2a** in the presence of Cs_2CO_3 was also observed, and the result demonstrates that base has no influence on the potential of reaction substrates (for detail, see fig. S2). Thereafter, EPR experiments were performed, as shown in Fig. 4B. Obviously, a distinct signal of a trapped radical by DMPO (5,5-dimethyl-1-pyrroline N-oxide) was detected when the reaction mixture of **1a** was carried out under electrochemical conditions. The parameters observed for the spin adduct are $g = 2.0068$, $A_H = 21.3$ G, and $A_N = 14.13$ G. We proposed that this radical signal belongs to a carbon radical. Moreover, no signal was observed in the reaction mixture of **2a**. However, we could not exclude the

existence of O-based radical from **2a**. This is because the O-based radical from **2a** is likely highly reactive and will likely do HAT (hydrogen atom transfer) with the solvent before reacting with DMPO.

On the basis of the above results, we proposed a mechanism for this electrochemical $C(sp^3)$—H etherification (Fig. 5). Indan is oxidized to aryl radical cation intermediate (**I**) via SET process. Second, **I** can resonate to form intermediate **II**, which generates **III** through the hydrogen abstraction by base. Subsequently, the resonance of **III** will form **IV**. Then, single-electron oxidation of **IV** can form the cation intermediate (**V**). Afterward, alcohols react with intermediate **V** to generate the **VI**, which will afford the desired product via the proton transfer process. Concomitant cathodic reduction generates hydrogen gas. In addition, an alternative mechanism in which the alcohol is oxidized to O-centered radical followed by HAT with the alkane cannot be excluded in this transformation.

CONCLUSION
In conclusion, an electrochemical, oxidant-free strategy for construction of C—O bonds through O—H/C(sp³)—H has been disclosed. A series of ethers were successfully accessed by using nonsolvent
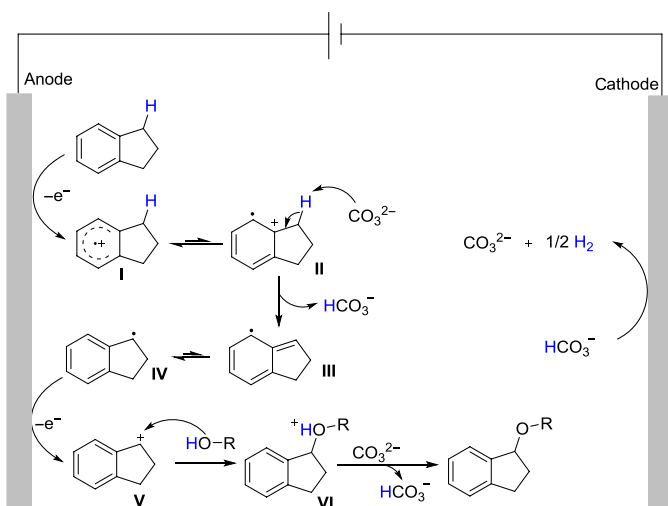
Fig. 5. Proposed mechanism.

amounts of alcohols as coupling partners, averting excessive waste of starting materials. Heteroatom-containing $C(sp^3)$—H compounds and cyclic olefins were also well tolerated. Mechanistically, the generation of aryl radical cation intermediates is the key to this $C(sp^3)$—H etherification, as evidenced by radical probe substrate (cyclopropane ring opening) and EPR experiments. This protocol provides not only a practical methodology for the synthesis of various ethers through $C(sp^3)$—H/O—H cross-coupling but also allows achieving direct electrochemical $C(sp^3)$—H functionalization in the absence of transition metal catalysis. Ongoing research including further mechanistic details and expanding the methodology to other heteroatom substrates is currently underway.

MATERIALS AND METHODS

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. The instrument for electrolysis is dual display potentiostat (DJS-292B) (made in China). The anodic electrode was graphite rod (ϕ 6 mm), and cathodic electrode was a platinum plate (15 mm by 15 mm by 0.3 mm) or nickel plate electrodes (15 mm by 15 mm by 1 mm). Thin-layer chromatography used glass 0.25-mm silica gel plates. Flash chromatography columns were packed with 200- to 300-mesh silica gel in petroleum (boiling point of 60° to 90°C). Gas chromatographic analyses were performed on SHIMADZU GC-2014 gas chromatography instrument with an flame ionization detector, and biphenyl was added as internal standard. Gas chromatography–mass spectrometry spectra were recorded on Varian GC MS 3900-2100T or SHIMADZU GC MS-2010. ^{1}H and ^{13}C nuclear magnetic resonance data were recorded with Bruker Advance III (400 MHz) spectrometers with tetramethylsilane as an internal standard.

General procedure for electrochemical oxidative etherification of indan

A 6-ml three-necked round-bottomed flask was charged with the Cs_2CO_3 (1 mmol, 2 equiv.) and $^nBu_4NClO_4$ (0.25 mmol, 0.5 equiv). The flask was equipped with a carbon rod anode (ϕ 6 mm) and a platinum plate (15 mm by 15 mm by 0.3 mm) or nickel plate elec-

trodes (15 mm by 15 mm by 1 mm) and then flushed with nitrogen. DCE (3 ml), indan (0.5 mmol, 1 equiv), phenethyl alcohol (1.5 mmol, 3 equiv), Et_2O (0.5 ml), and DCE (3 ml) were added in order. About 1.2 cm of the graphite rod was under the solution. The constant current (10 mA) electrolysis was carried out at 20°C for 3.5 hours. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with ethyl acetate/hexanes to give the product.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/20/eaaz0590/DC1

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