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Electrochemical dearomatization of 2-naphthols for C–O bond formation†

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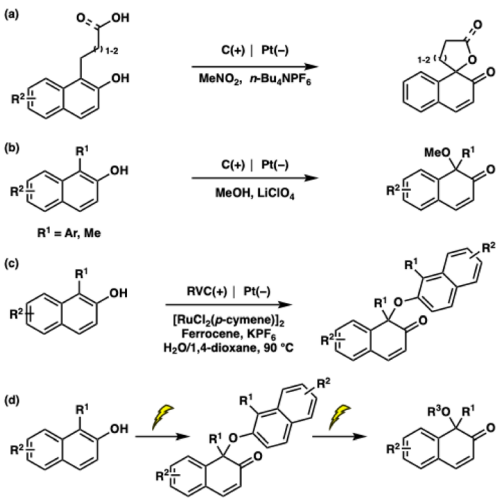
We reported a metal-free electrochemical oxidative C–O homocoupling of 2-naphthols, followed by subsequent alkoxylation under mild conditions. This strategy offered an eco-friendly and cost-effective electrochemical approach using undivided cells. Additionally, the reaction exhibited broad tolerance to various substituted 2-naphthols and diverse alcohols, affording the corresponding naphthalenones in moderate to good yields.

Naphthols and their derivatives are readily available chemical feedstocks that play crucial roles as valuable intermediates in synthetic chemistry.[1] In particular, the dearomatization of naphthol derivatives provides access to naphthalenone derivatives, which are frequently found in pharmaceuticals[2] and natural products.[3] Therefore, the development of efficient strategies for the dearomatization of naphthol derivatives has attracted significant interest from the synthetic community.[4] Although these achievements have been remarkable, most of the reaction conditions require oxidants or metal/organocatalysts. Recently, electrochemical dearomatizations of phenols and naphthols have been reported.[5,6] In 2023, Kalek and co-workers[5] developed electrochemical dearomatizing spirolactonization and spiroetherification methods for naphthols (Scheme 1a). In addition, electrochemical dearomative methoxylation reactions of naphthols or phenols were reported by the same research group in 2024 (Scheme 1b). However, C–O homocoupling products were not generated under these reaction conditions. Although the Liu group[6] reported electrochemical C–O homocoupling of 2-naphthols by oxidative dearomatization, the reaction required metal catalysts and high temperature (Scheme 1c). Herein, we discovered mild and metal-free electrochemical oxidative C–O homocoupling of 2-naphthols. Interestingly, the electrochemical alkoxylation of the C–O homocoupling product generated the alkoxylated naphthalenones (Scheme 1d).

1-Methyl-2-naphthol **1a** was used as a model substrate to optimize the reaction conditions (Table 1, see the ESI† for full optimization table). The reaction was conducted in a 1 : 1 mixture of MeCN and MeOH as the solvent, using an undivided cell under constant current conditions. The C–O homocoupled product **2a** was obtained in 44% yield at a constant current of 10 mA using a graphite cathode and a platinum anode (entry 1). The yield diminished when a platinum cathode and a graphite anode were employed (entry 2). We found that the reaction fared well with a platinum cathode and a platinum anode, providing the desired product **2a** in 74% yield (entry 3). Adjusting the current either to 5 mA or 15 mA, instead of 10 mA decreased yield of product **2a** (entries 4 and 5). An electrolyte screening revealed that the C–O homocoupling proceeded well when electrolytes containing bromide anions were used (entries 6–9). Among the bases screened, the addition of $NaHCO_3$ as a base additive led to an improved yield of the C–O homocoupled



Scheme 1 Electrochemical dearomative oxidation reactions of naphthols.

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† Electronic supplementary information (ESI) available: All experimental details, ^{1}H, ^{13}C NMR spectra, CV, and proposed mechanism. CCDC 2419735. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5ra02693h

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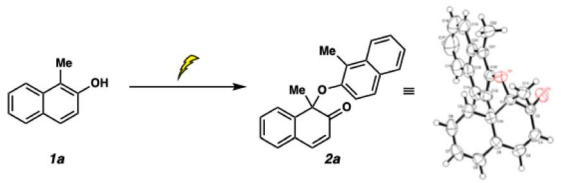
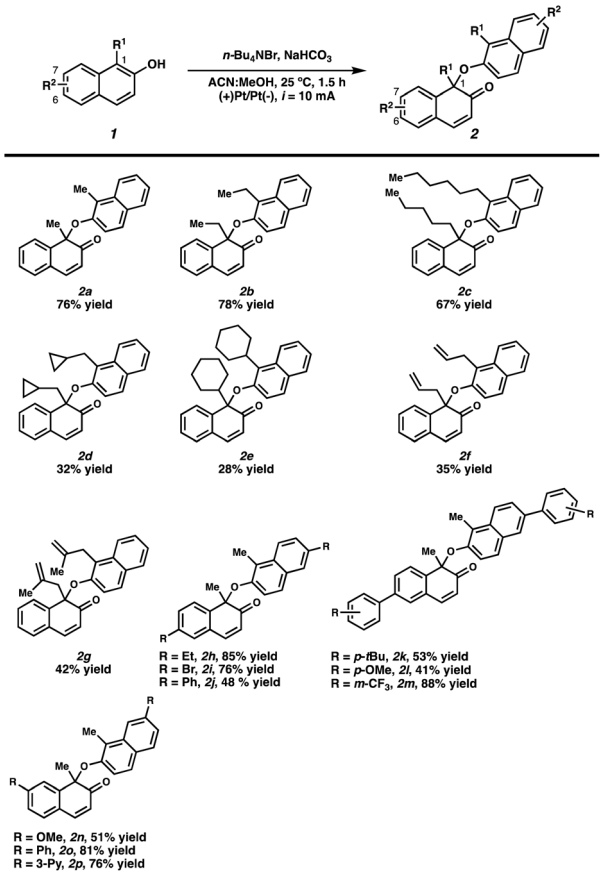
Table 1 Optimization of electrochemical oxidative C–O homocoupling reactions[a]



Entry	Electrode (+)/(−)	Electrolyte	I_{cell} (mA)	Additive (equiv.)	Yield[b] (%)
1	C/Pt	n-Bu_4NBF_4	10	—	44
2	Pt/C	n-Bu_4NBF_4	10	—	18
3	Pt/Pt	n-Bu_4NBF_4	10	—	74
4	Pt/Pt	n-Bu_4NBF_4	5	—	35
5	Pt/Pt	n-Bu_4NBF_4	15	—	40
6	Pt/Pt	n-Bu_4NPF_6	10	—	38
7	Pt/Pt	LiBr	10	—	74
8	Pt/Pt	NaBr	10	—	75
9	Pt/Pt	n-Bu_4Br	10	—	79
10	Pt/Pt	n-Bu_4Br	10	$NaHCO_3$ (0.5)	80
11	Pt/Pt	n-Bu_4Br	10	$NaHCO_3$ (1.5)	96
12	Pt/Pt	n-Bu_4Br	10	$NaHCO_3$ (3.0)	75
13	Pt/Pt	n-Bu_4Br	—	$NaHCO_3$ (1.5)	–[c]

[a] Reaction conditions: 1-methyl-2-naphthol **1a** (0.32 mmol, 1.00 equiv.) and electrolyte (0.32 mmol, 1.00 equiv.) were dissolved in MeCN : MeOH (1 : 1, 0.05 M) and subjected to electrochemistry in an undivided cell under constant current conditions. [b] Determined by high-performance liquid chromatography (HPLC) using 3-nitrophenol as an internal standard. [c] Not observed.



Scheme 2 Substrate scope of substituted-2-naphthol for homocoupling reactions.[a,b] [a] Reaction conditions: 1-substituted-2-naphthol **1a** (0.16 mmol, 1.00 equiv.), n-Bu_4NBr (0.16 mmol, 1.00 equiv.) and $NaHCO_3$ (0.24 mmol, 1.50 equiv.) were dissolved in MeCN : MeOH (1 : 1, 0.05 M) and subjected to electrochemistry in an undivided cell under constant current conditions. [b] The yield is that of the isolated product.

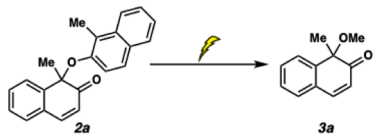
product **2a** (entries 10–12; see the ESI† for details). The desired product **2a** was not observed in the absence of an electric current (entry 13). The structure of **2a** was unambiguously confirmed by a X-ray diffraction analysis.

With the optimized conditions in hand, we explored the substrate scope of the electrochemical oxidative C–O homocoupling reactions (Scheme 2). Naphthols with linear alkyl substitutions at C(1) generated the corresponding products in good yields (**2a–2c**). Cyclopropylmethyl and cyclohexyl substitutions at the C(1) position of the 2-naphthols generated the desired products in lower yields (**2d** and **2e**). In addition, allyl substitutions at the C(1) position of 2-naphthols were tolerated under our reaction conditions, producing the corresponding products in 35% and 42% yields, respectively (**2f** and **2g**). We also investigated the substrate scope of the substitutions at the C(6) and C(7) positions of 1-methyl-2-naphthols. 1-Methyl-2-naphthols bearing ethyl, bromo, and phenyl substituents on C(6) afforded the corresponding products in moderate to good yields (**2h**, **2i**, and **2j**). The electronically variable aryl groups in C(6) were compatible with the reaction conditions (**2k–2m**). In addition, 1-methyl-2-naphthols bearing a methoxy substituent at the C(7) position provided **2n** in 51% yield. Phenyl- and pyridine-substituted 1-naphthols were well tolerated, furnishing the corresponding products in good yields (**2o** and **2p**).

We observed trace amounts of 1-methoxy-1-methyl-naphthalenone **3a** were generated during the electrochemical dearomative C–O homocoupling reaction. Notably, 1-methoxy-1-methyl-naphthalenone **3a** was detected only in the final stages of the reaction, whereas **3a** was not observed at the beginning. Thus, we hypothesized that **3a** could be produced from C–O homocoupling product **2a**. We then attempted to optimize the reaction conditions for the methoxylation of **2a** to obtain 1-methoxy-1-methyl-naphthalenone **3a** (Table 2, see more details in ESI†). The yield of methoxylated naphthalenone **3a** increased as the reaction current was decreased (entries 1–3). The addition of Na_2HPO_4 as a base additive produced methoxy **3a** in a yield similar to that obtained with $NaHCO_3$ (entries 3 and 4).[7] However, the addition of excess Na_2HPO_4 resulted in a lower yield of **3a** (entries 4–6). Altering the anode to either graphite or nickel was detrimental to the yield (entries 7 and 8). A survey of the different electrolytes revealed that n-Bu_4NBF_4 was the optimal electrolyte (entries 9 and 10). Desired product **3a** was not detected in the absence of an electric current (entry 11).

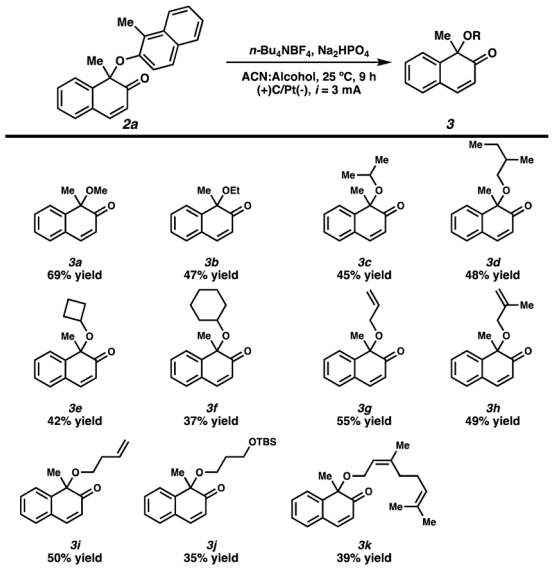
We investigated the substrate scope of alcohols to obtain alkoxylated **2a** (Scheme 3). In addition to the simple methoxy

Table 2 Optimization of electrochemical alkoxylation reactions[a]



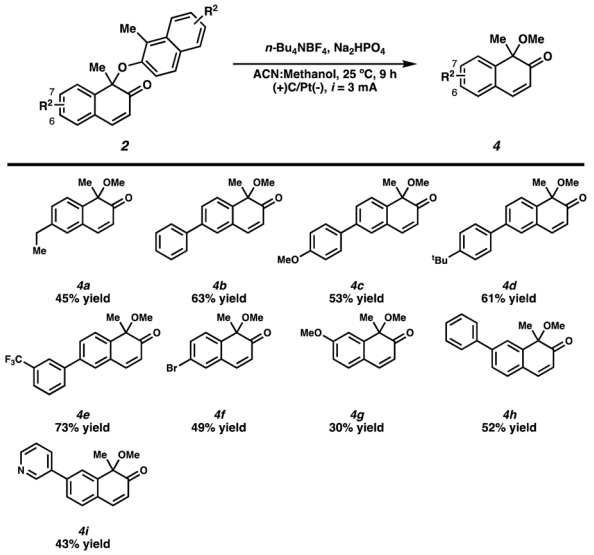
Entry	Electrode (+)/(−)	Electrolyte	I_{cell} (mA)	Additive (equiv.)	Yield[b] (%)
1	C/Pt	n-Bu_4NPF_6	10	$NaHCO_3$ (0.5)	60[b]
2	C/Pt	n-Bu_4NPF_6	5	$NaHCO_3$ (0.5)	64[b]
3	C/Pt	n-Bu_4NPF_6	3	$NaHCO_3$ (0.5)	66[b](51[c])
4	C/Pt	n-Bu_4NPF_6	3	Na_2HPO_4 (0.5)	66[b](52[c])
5	C/Pt	n-Bu_4NPF_6	3	Na_2HPO_4 (1.0)	61[c]
6	C/Pt	n-Bu_4NPF_6	3	Na_2HPO_4 (1.5)	45[b]
7	C/C	n-Bu_4NPF_6	3	Na_2HPO_4 (1.0)	47[c]
8	C/Ni	n-Bu_4NPF_6	3	Na_2HPO_4 (1.0)	57[c]
9	C/Pt	n-Bu_4NBF_4	3	Na_2HPO_4 (1.0)	69[c]
10	C/Pt	$NaBF_4$	3	Na_2HPO_4 (1.0)	59[c]
11	C/Pt	n-Bu_4NBF_4	—	Na_2HPO_4 (1.0)	–[d]

[a] Reaction conditions: compound **2a** (0.32 mmol, 1.00 equiv.) and the electrolyte (0.32 mmol, 1.00 equiv.) were dissolved in MeCN : MeOH (1 : 1, 0.05 M) and subjected to electrochemistry in an undivided cell under constant current conditions. [b] Determined by ^{1}H NMR using BHT as an internal standard. [c] Isolated yield. [d] Not observed.



Scheme 3 Substrate scope of diverse alkoxylation reactions.[a,b] [a] Reaction conditions: 1-methyl-1-((1-methylnaphthalen-2-yl)oxy) naphthalen-2(1*H*)-one **2a** (0.16 mmol, 1.00 equiv.), n-Bu_4NBF_4 (0.16 mmol, 1.00 equiv.) and Na_2HPO_4 (0.16 mmol, 1.00 equiv.) were dissolved in MeCN : MeOH (1 : 1, 0.05 M) and subjected to electrochemistry in an undivided cell under constant current conditions. [b] The yield is that of the isolated product.

group, ethoxy, isopropoxy, and butoxy-substituted naphthalenones (**3a–3d**) were generated in moderate yields under our reaction conditions. In addition, cyclobutyloxy- and cyclohexyloxy-substituted naphthalenones were generated in

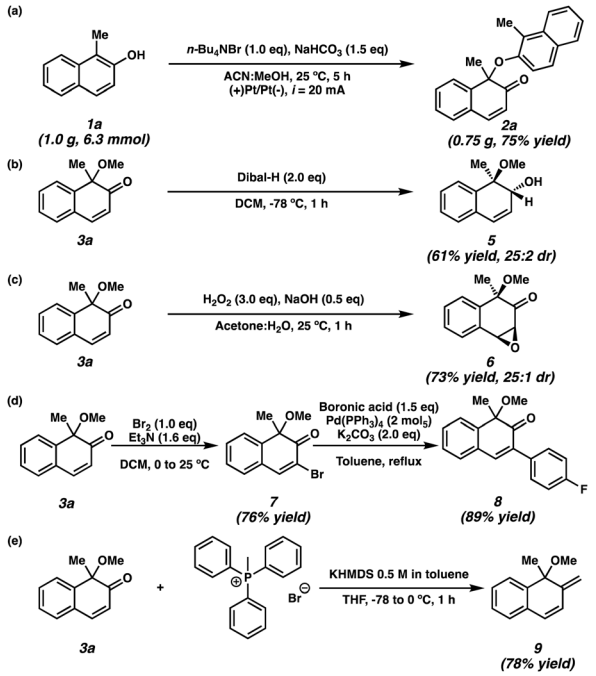


Scheme 4 Substrate scope of methoxylation reactions.[a,b] [a] Reaction conditions: substituted-2-naphthol dimer **2** (0.16 mmol, 1.00 equiv.), n-Bu_4NBF_4 (0.16 mmol, 1.00 equiv.) and Na_2HPO_4 (0.16 mmol, 1.00 equiv.) were dissolved in MeCN : MeOH (1 : 1, 0.05 M) and subjected to electrochemistry in an undivided cell under constant current conditions. [b] The yield is that of the isolated product.

42% and 37% yields, respectively. The use of allyl and homoallyl alcohols afforded the corresponding products in moderate yields (**3g–3i**). The silyl ether functional group was tolerated under our reaction conditions, producing **3j** in 35% yield. Additionally, the use of geraniol as a substrate generated **3k** in 39% yield.

Next, the substrate scope of the C(6) and C(7) substituents was explored in the methoxylation reactions (Scheme 4). The substrate bearing an ethyl substituent at C(6) afforded **4a** in 45% yield. In addition to the simple phenyl substituent, aryl substituents with electron-donating or electron-withdrawing groups fared well under the reaction conditions, affording the corresponding products in good yields (**4b–4e**). In addition, a bromo substituent on C(6) was tolerated under the reaction conditions furnishing **4f** in 49% yield. Substrates containing methoxy and aryl substituents on C(7) produced the corresponding products in moderate yields (**4g–4i**).

To demonstrate the synthetic utility of our reaction, we performed a gram-scale synthesis, generating the desired product **2a** in 75% yield, although a current of 20 mA was required for full conversion. Unfortunately, scaling up the alkoxylation of dimer **2a** to the gram scale resulted in poor conversion under the optimized conditions. Moreover, reduction of ketone **3a** with DIBAL produced alcohol **5** in 61% yield with high diastereoselectivity.[8] Treatment of α,β-unsaturated ketone **3a** with H_2O_2 afforded epoxide **6** in 73% yield with high diastereoselectivity.[9] In addition, bromination of α,β-unsaturated ketone **3a** with bromine provided **7**, and a subsequent Suzuki coupling reaction with 4-fluorophenylboronic acid generated **8** in 89% yield.[10] Alkene **9** was synthesized in 78% yield *via* the Wittig reaction of ketone **3a** with methyltriphenylphosphonium bromide (Scheme 5).[11]



Scheme 5 Gram scale and diversification.

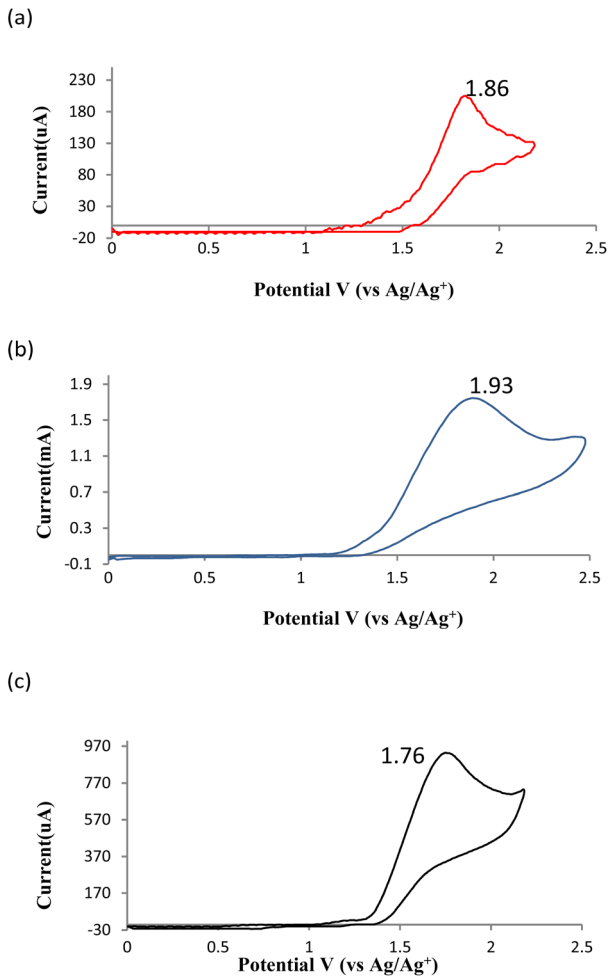


Fig. 1 (a) **1a** in 0.1 M nBu$_4$NBF$_4$ in ACN, (b) **2a** in 0.1 M nBu$_4$NBF$_4$ in ACN, (c) **2a** + Na_2HPO_4 in 0.1 M nBu$_4$NBF$_4$ in ACN.

1-Methylnaphthalen-2-ol **1a** exhibited an oxidation peak at 1.86 V (*vs.* Ag/AgCl) (Fig. 1a). 1-Methyl-1-((1-methylnaphthalen-2-yl)oxy)naphthalen-2(1*H*)-one **2a** showed a slightly higher oxidation peak at 1.93 V (Fig. 1b). Upon the addition of a base to the solution of **2a**, the oxidation potential decreased to 1.76 V (*vs.* Ag/AgCl) (Fig. 1c), indicating that the presence of base facilitated the oxidation of **2a**.

Conclusions

In summary, we have developed an efficient and sustainable electrochemical oxidative dearomatization of 2-naphthols, achieving C–O homocoupling and subsequent alkoxylation under mild and metal-free conditions. The optimized reaction conditions afforded the corresponding naphthalenone in moderate to good yields with broad functional group compatibility. Moreover, the utility of our products was demonstrated through gram scale and derivatization of the synthesized naphthalenones. Thus, this study provides environmentally friendly electrochemical oxidative approaches and shows potential for the synthesis of pharmaceuticals and natural product scaffolds.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for **2a** has been deposited at the CCDC under 2419735.

Author contributions

Han Byeol Kim: data curation, investigation, methodology, and writing – original draft. Dong Kyun Han: data curation, investigation, methodology, and writing – original draft. Jae Kyun Lee: data curation. Seo-Jung Han: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, writing – original draft, and writing – review and editing.

Conflicts of interest

The authors declare no competing interests.

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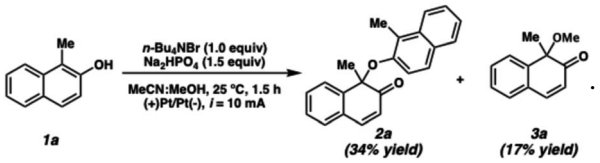
7 Upon employing Na_2HPO_4 as an additive for the reaction of 1-methyl-2-naphthol **1a**, both C–O homocoupled **2a** and alkoxylated 3a were obtained in 34% and 17%, respectively. These results indicate that the direct synthesis of the alkoxylated compound from 1-methyl-2-naphthol using Na_2HPO_4 as an additive is challenging



1a 2a (34% yield) 3a (17% yield)

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