Sequential Paired Electrochemical Transformation of Styrene Oxide via Anodic Meinwald Rearrangement and Cathodic Nitromethylation in an Electrochemical Flow Reactor with Catalytic Electrical Input

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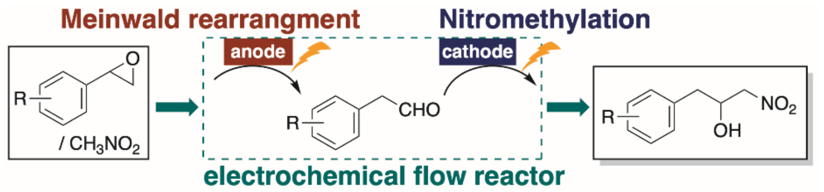

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Abstract Paired electrosynthesis, which utilize both anodic and cathodic events in electrolysis, enables attractive transformations with higher current efficiency than conventional electrosynthesis. The electrochemical flow technique has been widely employed to ensure stable reaction conditions and mitigate issues stemming from mass transfer. In this study, we investigated the electrochemical Meinwald rearrangement of styrene oxides, yielding aldehydes as intermediates, followed by the nitromethylation of aldehydes to produce β-nitro alcohols. These reactions were achieved with catalytic electrical input, enabling the conversion of various styrene oxides into the corresponding β-nitro alcohols.

Key words Electrochemical organic synthesis, Paired electrolysis, Meinwald rearrangement, Nitromethylation, Flow synthesis

Electrochemical organic synthesis has garnered attention as a powerful tool in organic chemistry, wherein electricity can activate various organic compounds.[1] The externally supplied electricity sometimes generates ionic or radical species that are not readily available using the typical chemical reagents. Moreover, electrochemical synthesis is esteemed for its environmentally friendly attributes. The anodic oxidation and cathodic reduction can lower the need for chemical oxidants and reductants, which are often toxic, hazardous, and explosive reagents. Despites the recognized advantages of organic electrolysis, electrochemical synthesis typically occurs at only one electrode, either an anode or a cathode. Consequently, one electrode of a pair is usually underutilized for useful organic transformations, resulting in the wastage of side products.

In contrast, paired electrosynthesis harnesses both anodic and cathodic events in electrolysis, enhancing energy efficiency.[2] In 1976, Baizer demonstrated the early concept of paired electrolysis,[3] illustrating co-electrolysis of ethyl acrylate and diethyl malonate to yield diethyl adipate at the cathode and tetraethyl ethane-1,1,2,2-tetracarboxylate at the anode. This type of parallel paired electrolysis, wherein two different transformations occur in an undivided cell, one per each electrode, is depicted in Figure 1-I. Another process that has been explored is convergent paired electrolysis, wherein both anodic- and cathodic-generated intermediates react to afford the desired compound (Figure 1-II). For instance, Hilt reported the convergent electrochemical synthesis of formamide-protected homoallylic alcohols.[4] The reaction between the allylic anion and benzaldehyde generated an alkoxide on the cathode, which then reacted with an iminium ion, generated on the anode, to yield the protected homoallylic alcohol. Sequential electrochemical synthesis has also garnered attention (Figure 1-III). An electrochemical oxidation-reduction sequence of oximes to yield nitriles was reported by Waldvogel in 2015.[5] They demonstrated that the anodic oxidation of oximes yielded nitrile oxide, which was subsequently transformed into nitrile via cathodic reduction.

Although impressive transformations based on paired electrolysis exist, the slow mass transfer of activated compounds between two electrodes sometimes constrains the reaction scope of paired electrolysis. One simple solution to this issue is alternating current (AC) electrolysis (Figure 1-IV).[6] In AC electrolysis, alternating voltage is applied to the reaction solution, with oxidation and reduction occurring on the same surface. Short-lived intermediates can be handled without decomposition since they can bypass the mass transfer issue. However, generating the ideal waveform, such as a complete square wave, is challenging, and the applied voltage fluctuates during electrolysis. Consequently, achieving precise reaction control is often difficult in AC electrolysis.

Conversely, the electrochemical flow technique[7] has also found application in paired electrolysis.[8] In 2005, Yoshida and Suga reported that the electrochemical flow system enables paired electrolysis,[8b] generating electrophiles on the anode and nucleophiles on the cathode. Both short-lived intermediates can react with each other after electrolysis. Recently, Buchwald and Jensen achieved single electron transfer-promoted redox-neutral C–C bond formation using an electrochemical flow system.[8f] When the undivided flow system is employed, the flow reactor minimizes the distance between two electrodes, thereby preventing the decomposition of unstable intermediates during mass transfer. Moreover, the divided flow system can also be suitable for paired electrolysis. In this system, the electrolyzed solution can be immediately discharged after the first electrolysis. Once the solution is pumped to the other electric chamber, paired electrolysis can be completed (*vide infra*). Compared to AC electrolysis, the electrochemical flow technique can precisely control reaction conditions, including time, applied current, and temperature, though appropriate flow devices must be designed.

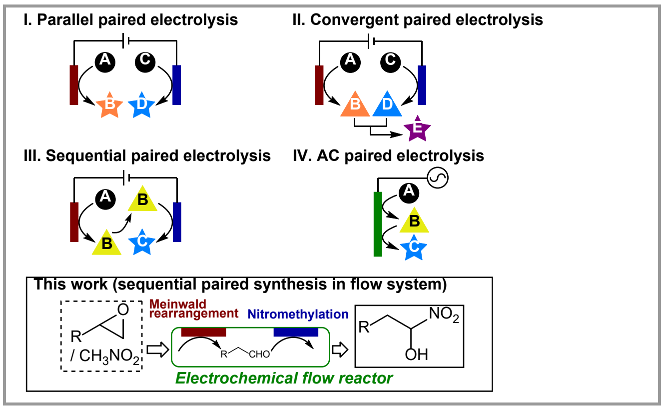
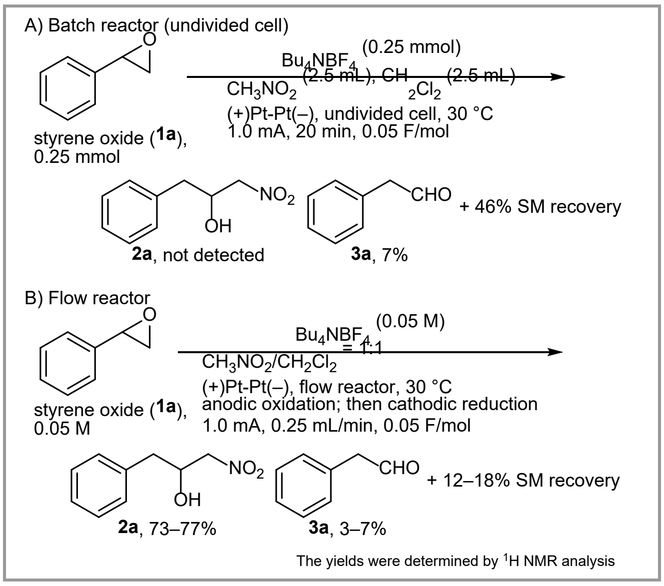


Figure 1. Paired electrosynthesis.

We have investigated electrochemical synthesis using flow devices, achieving several transformations initiated by catalytic electricity with a small flow cell.[9] In this context, we focused on sequential paired electrochemical synthesis initiated by catalytic electrical input. Specifically, we investigated the cathodic transformation of aldehydes, such as cyanosilylation[9a] and alkynylation.[10] Therefore, we anticipate that the cathodic transformation of aldehydes could be feasible if aldehydes were generated by an anodic reaction. In 1983, Torii reported that the electrochemically generated acid on the anode can catalyze the Meinwald rearrangement[11] (one of the 1,2-shifts of the alkyl group) of epoxides to yield aldehydes.[12] We subsequently combined the anodic Meinwald rearrangement with the cathodic transformation of aldehydes. For the cathodic event, we selected cathodically induced nitromethylation, initially reported by Elinson in 2008.[13] More recently, Tajima demonstrated the paired electrolysis of benzyl alcohol in an undivided cell, which enabled the anodic generation of benzaldehyde followed the cathodic nitormethylation.[14] Therefore, sequential electrochemical synthesis of the corresponding β-nitro alcohols using the anodic Meinwald rearrangement and the subsequent cathodic addition reaction, both of which should be facilitated by a catalytic amount of electricity (Figure 1, bottom), emerges as a promising technique.

Initially, we performed the Meinwald rearrangement of styrene oxide (**1a**) followed by the cathodic addition reaction of nitromethane (Scheme 1). Using a batch-type undivided electrochemical cell did not yield the β-nitro alcohol **2a** (Scheme 1A). Small amounts of aldehyde **3a**, resulting from the anodic stage, were observed (7%), and the starting material **1a** was primarily recovered (46%). The reaction sequence would proceed with electro-generated acid (EGA) and electro-generated base (EGB), and these species should be neutralized by each other. As a result, the batch system did not convert enough of the starting material. In contrast, using the electrochemical flow reactor yielded a significant amount of β-nitro alcohol **2a** (73–77%, Scheme 1B). The electrochemical flow reaction was conducted using the following setup (Figure 2): a solution of styrene oxide (**1a**, 0.05 M) and tetrabutylammonium tetrafluoroborate (0.05 M) in the mixed solvent of nitromethane and dichloromethane (1:1) was passed into the electrochemical flow cell. Next, the solution was oxidized in an anodic chamber, while the discharged solution was immediately transferred into a cathodic chamber and electrochemically reduced. The electrolyzed solution was finally collected, and ^{1}H nucleaer magnetic resonance (NMR) analysis was used to determine the yields. This system facilitated sequential electrolysis achieved by separated anodic and cathodic events (*vide supra*).



Scheme 1. The comparison of the batch and the flow reactor.

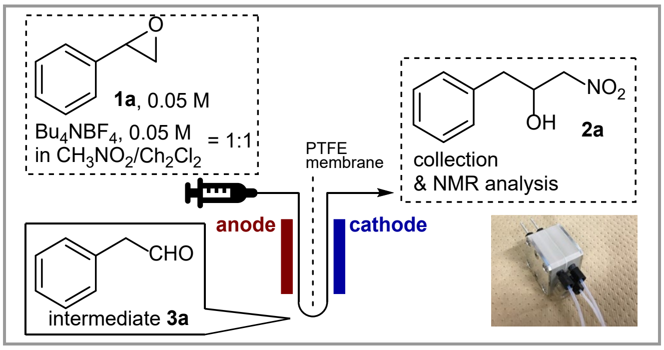
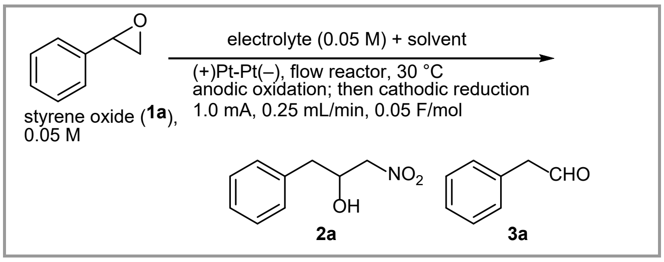


Figure 2. The whole setup for the electrochemical flow reactor.

We also investigated the effect of the solvent and electrolyte (Table 1). Although using nitromethane alone without dichloromethane yielded a moderate amount of β-nitro alcohol

2a, reproducibility was not confirmed (56–77%, entry 1), and the yield range was significant broader compared to using mixed solvents (Scheme 1B). While employing a nitromethane/tetrahydrofuran (THF) mixture as a solvent could yield β-nitro alcohol **2a** (35%, entry 2), other solvents such as dimethylformamide (DMF, entry 3), dimethyl sulfoxide (DMSO, entry 4), and ethanol (EtOH, entry 5) could not. Additionally, phenylacetaldehyde **3a**, the potential intermediate, was not detected when unsuccessful mixed solvents were used. This disparity when using different solvents could be attributed to the properties of the electro-generated acid, with the heightened acidity in the presence of dichloromethane[15] being crucial in the sequential reactions. Tetrabutylammonium tetrafluoroborate was essential as an electrolyte to yield a significant amount of β-nitro alcohol **2a**. When corresponding hexafluorophosphate (entry 6), perchlorate (entry 7), and triflate (entry 8) were selected instead of tetrafluoroborate, a slight decrease in the yields of β-nitro alcohol **2a** was observed.

Table 1. The effect of solvents and electrolytes.

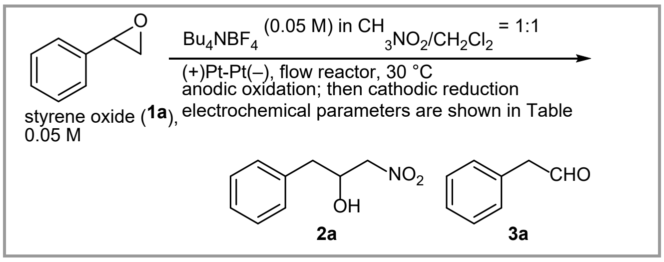


entry	electrolyte	solvent	2a (%)^a	3a (%)
1	Bu_4NBF_4	CH_3NO_2	56–77	15–18
2	Bu_4NBF_4	CH_3NO_2/THF = 1:1	35	18
3	Bu_4NBF_4	CH_3NO_2/DMF = 1:1	N.D.^{b}	N.D.
4	Bu_4NBF_4	CH_3NO_2/DMSO = 1:1	N.D.	N.D.
5	Bu_4NBF_4	CH_3NO_2/EtOH = 1:1	N.D.	N.D.
6	Bu_4NPF_6	CH_3NO_2/CH_2Cl_2 = 1:1	8	N.D.
7	Bu_4NClO_4	CH_3NO_2/CH_2Cl_2 = 1:1	23	50
8	Bu_4NOTf	CH_3NO_2/CH_2Cl_2 = 1:1	42	39

(a) The yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. (b) Not detected.

The electrochemical conditions were then optimized (Table 2). Decreasing or increasing the flow rate of the reaction solution under constant electric current resulted in decreased yield of β-nitro alcohol **2a** (entries 1–3). A lower flow rate caused increased electricity, leading to undesired side reactions. Conversely, a higher flow rate resulted in less electricity, with the major problem being reduced reaction time. In this case, phenylacetaldehyde (**3a**), an intermediate after anodic oxidation, was recovered (entries 1 vs.3). Reduction of the current value also led to a lower yield of β-nitro alcohol **2a** (entries 3 vs. 4). Increasing the current value to 2.0 mA (entry 5) resulted in the highest yield of β-nitro alcohol **2a**. Moreover, when a higher concentration of the starting material was required due to productivity issue, the combination of a higher current value and lower flow rate, which could generate sufficient electricity, yielded a significant amount of β-nitro alcohol (entry 6). Thus, finely adjusting the electrochemical conditions is rendered essential to maintain the efficiency of both anodic and cathodic transformation.

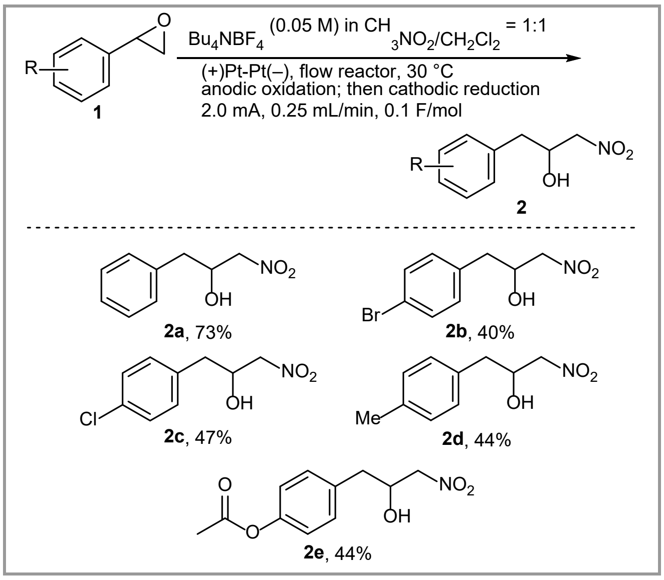
Table 2. Optimization of the electrochemical parameters.



entry	current (mA)	flow rate (mL/min)	electricity (F/mol)	2a (%)^a	3a (%)
1^b	1.0	0.25	0.05	73–77	3–7
2	1.0	0.13	0.1	53	41
3	1.0	0.50	0.03	34	23
4	0.5	0.50	0.01	12	1
5	2.0	0.25	0.1	78 (73)^c	7
6^d	4.0	0.13	0.2	76	trace

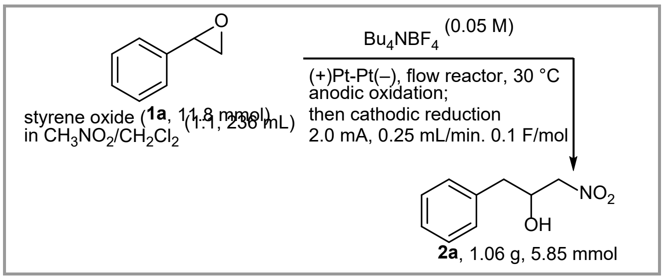
(a) The yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. (b) The same conditions and results were described in Scheme 1B. (c) Isolated yield. (d) 0.1 M of styrene oxide (**1a**) was used.

With optimized reaction conditions for paired electrolysis at hand, proceeded to perform sequential synthesis of β-nitro alcohols from various styrene oxide derivatives (Scheme 2). The sequential transformation of styrene oxides with halogen atoms yielded moderate amounts of corresponding β-nitro alcohols **2b** and **2c**. During the purification on silica gel, electron-withdrawing groups facilitated dehydration, leading to observed decomposition of β-nitro alcohols. Furthermore, Meinwald rearrangement and nitromethylation sequence progressed with electron-donating methyl and acetoxy groups. Styrene oxides **1d** and **1e** as starting materials yielded moderate quantities of β-nitro alcohols.



Scheme 2. Substrate scope.

Finally, we explored gram-scale synthesis of β-nitro alcohol (Scheme 3). A total of 236 mL of styrene oxide solution in CH_3NO_2/CH_2Cl_2 was passed into the electrochemical flow reactor, and a constant current of 2.0 mA was applied. Consequently, 1.06 g of desired β-nitro alcohol **2a** was obtained, with no significant decrease in yield observed during the large-scale synthesis using our electrochemical flow reactor.



Scheme 3. Gram-scale synthesis

The Meinwald rearrangement and nitromethylation sequence would proceed through the mechanism described in Figure 3. First, anodic oxidation generates electro-generated acid (EGA), and EGA reacts with styrene oxide, and the ring-opening of the epoxide affords benzylic cation **B**—the benzylic cation intermediate proceeds 1,2-shift of the hydrogen atom, which gives aldehyde **3a**. Then, aldehyde **3a** is transferred to the cathodic chamber, and nucleophilic attack of nitromethyl anion, which is generated by the electro-generated base (EGB)-assisted deprotonation of nitromethane, affords alkoxide **C**.[14] Finally, the deprotonation of nitromethane by alkoxide **C** regenerates nitromethyl anion, which would allow the reaction to proceed with a catalytic amount of electricity. The reaction should not proceed unless the amount of EGB produced in the anodic chamber exceeds the amount of EGA produced. The generation of EGA would depend on the amount of trace water,[11] and its activity is very high. Details are not clear, but only a small amount of electricity is used for EGA generation, and excess electricity would be consumed by oxidation of the other compounds, such as electrolytes and the starting material. Therefore, the reaction probably proceeded because more EGB was produced than EGA, even though an equivalent amount of electricity was used at the anode and cathode.

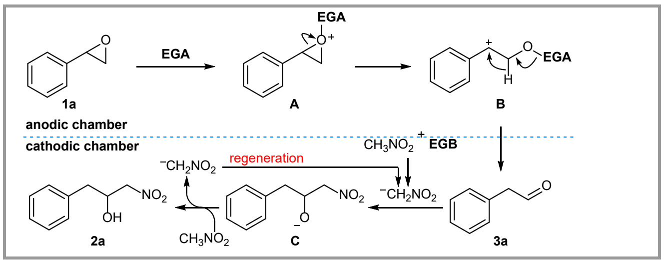


Figure 3. Plausible reaction mechanism

In conclusion, we have developed sequential flow electrolysis of styrene oxide derivatives, enabling the consecutive occurrence of Meinwald rearrangement and nitromethylation of aldehydes. The transformation required catalytic electrical input to achieve higher current efficiency.

General Remarks

NMR spectra were obtained using JEOL ECS-400 (^1H 400 MHz, ^{13}C 100 MHz) and JEOL JMN-ECZ600R (^1H 600 Hz, ^{13}C 150 MHz) spectrometers. Chemical shifts for ^1H NMR were reported in parts per million (ppm) relative to tetramethyl silane (δ 0.00 ppm). Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad signal). Chemical shifts for ^{13}C NMR were reported in parts par million (ppm) relative to $CDCl_3$ (δ 77.16 ppm) with complete proton decoupling. Infrared (IR) spectra and high-resolution mass spectra (HRMS) were recorded with a SHIMADZU IRAffinity-1 spectrometer and a Bruker Daltonics microTOF II, respectively. Flash chromatography was carried out on KANTO CHEMICAL Silica gel 60N (40–50 μm). Electrochemical flow reactors were purchased from DFC Co., Ltd. (FC-ECR-1.0).

Materials

Unless otherwise noted, all materials were purchased from commercial suppliers and used without further purification. Dichloromethane (CH_2Cl_2) was washed with water, distilled from P_4O_{10}, and redistilled from CaH_2 to remove trace amounts of acid, and stored over MS4A. Nitromethane (CH_3NO_2) was stored over MS4A. Styrene oxide derivatives **1b**,[16] **1d**,[17] and **1e**[18] were synthesized from corresponding styrene derivatives by epoxidation.

Sequential Electrolysis

Bu_4NBF_4 (0.05 M) and styrene oxide (**1**, 0.05 M) were dissolved in a mixed solvent (CH_3NO_2/CH_2Cl_2 = 1:1). The solution pumped by a syringe pump (YMC, YSP-301) into an electrochemical flow reactor. First, anodic oxidation was carried out, and the solution was transferred to the cathodic chamber for cathodic reduction. A constant current (2.0 mA) was applied with a flow rate of 0.25 mL/min, consuming 0.1 F/mol of electricity. The resulting mixture (2.0 mL) was collected, and concentrated *in vacuo*. NMR yields were calculated by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Subsequently, the crude product was purified by column chromatography on SiO_2 to yield β-nitro alcohol **2**.

1-Nitro-3-phenyl-propan-2-ol (2a)[19]

The compound **2a** was obtained by column chromatography on SiO_2 (hexane/EtOAc = 3:1).

Yield: 13.2 mg (0.073 mmol, 73%); colorless liquid.

^1H NMR (600 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 7.3, 7.0 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.0 Hz, 2H), 4.58 (m, 1H), 4.44 (dd, *J* = 3.1, 13.2 Hz, 1H), 4.40 (*J* = 8.5, 13.2 Hz, 1H), 2.91 (dd, *J* = 7.3, 13.8 Hz, 1H), 2.84 (dd, *J* = 6.2, 13.8 Hz, 1H), 2.49 (brs, 1H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 135.9, 129.5, 129.1, 127.5, 79.8, 69.6, 40.5.

IR (neat): 3543, 3417, 3030, 2926, 1552, 1385, 1090, 702 cm^{-1}.

1-Nitro-3-(4-bromophenyl)-propan-2-ol (2b)

The compound **2b** was obtained by column chromatography on SiO_2 (hexane/EtOAc = 3:1).

Yield: 10.7 mg (0.041 mmol, 40%); colorless liquid.

^1H NMR (600 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.54 (m, 1H), 4.37 (dd, *J* = 3.1, 13.4 Hz, 1H), 4.39 (dd, *J* = 8.4, 13.4 Hz, 1H), 2.84 (dd, *J* = 7.6, 14.1 Hz, 1H), 2.80 (dd, *J* = 5.7, 14.1 Hz, 1H), 2.51 (brs, 1H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 135.0, 132.1, 131.2, 121.4, 79.7, 69.3, 39.7.

IR (KBr): 3358, 3291, 2938, 1557, 1489, 1381, 1107, 1012, 808 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_9H_{10}BrNaNO_3$ $[M+Na]^+$ 281.9736, found 281.9735.

Melting point: 55.7–57.1 °C.

1-Nitro-3-(4-chlorophenyl)-propan-2-ol (2c)

The compound **2c** was obtained by column chromatography on SiO_2 (hexane/EtOAc = 3:1).

Yield: 9.2 mg (0.043 mmol, 47%); colorless liquid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 4.54 (m, 1H), 4.44 (dd, *J* = 2.9, 13.5 Hz, 1H), 4.39 (dd, *J* = 8.4, 13.5 Hz, 1H), 2.86 (dd, *J* = 7.5, 13.9 Hz, 1H), 2.82 (dd, *J* = 5.7, 13.9 Hz, 1H), 2.52 (brs, 1H, OH).

^{13}C NMR (150 Hz, $CDCl_3$): δ 134.5, 133.4, 130.8, 129.2, 79.7, 69.4, 39.7.

IR (neat): 3526, 3433, 2926, 1557, 1493, 1385, 1092, 1016, 808 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_9H_{10}ClNaNO_3$ $[M+Na]^+$ 238.0241, found 238.0242.

1-Nitro-3-(4-methylphenyl)-propan-2-ol (2d)

The compound **2d** was obtained by column chromatography on SiO_2 (hexane/EtOAc = 3:1).

Yield: 7.6 mg (0.039 mmol, 39%); colorless liquid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.15 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 4.55 (m, 1H), 4.43 (dd, *J* = 3.2, 13.2 Hz, 1H), 4.39 (dd, *J* = 8.7, 13.2 Hz, 1H), 2.86 (dd, *J* = 7.3, 13.8 Hz, 1H), 2.80 (dd, *J* = 8.6, 13.8 Hz, 1H), 2.45 (brs, 1H, OH), 2.34 (s, 3H).

^{13}C NMR (150 Hz, $CDCl_3$): δ 137.2, 132.7 129.8, 129.3, 79.8, 69.7, 40.1, 21.2.

IR (neat): 3543, 3445, 2924, 2594, 2351, 1557, 1516, 1385, 1086, 808 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{10}H_{13}NaNO_3$ $[M+Na]^+$ 218.0788, found 218.0776.

1-Nitro-3-(4-acetoxyphenyl)-propan-2-ol (2e)

The compound **2e** was obtained by column chromatography on SiO_2 (hexane/EtOAc = 3:1).

Yield: 10.3 mg (0.043 mmol, 44%); colorless liquid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 4.56 (m, 1H), 4.45 (dd, *J* = 3.0, 13.5 Hz, 1H), 4.41 (dd, *J* = 8.5, 13.5 Hz, 1H), 2.88 (dd, *J* = 7.5, 13.8 Hz, 1H), 2.84 (dd, *J* = 5.9, 13.8 Hz, 1H), 2.51 (brs, 1H, OH), 2.31 (s, 3H).

^{13}C NMR (150 Hz, $CDCl_3$): δ 169.7, 150.0, 133.6, 130.5, 122.2, 79.7, 69.5, 39.8, 21.3.

IR (neat): 3480, 3460, 2928, 1755, 1533, 1506, 1196, 1018 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{11}H_{13}NaNO_5$ $[M+Na]^+$ 262.0686, found 262.0667.

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Supporting Information

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Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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