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# TEMPO-Mediated Electrochemical N-demethylation of Opiate Alkaloids

Ali Alipour Najmi,<sup>[a]</sup> M. Faizan Bhat,<sup>[b]</sup> Rainer Bischoff,<sup>[a]</sup> Gerrit J. Poelarends,<sup>[b]</sup> and Hjalmar P. Permentier<sup>\*[a]</sup>

A new TEMPO-mediated electrochemical method has been developed for N-demethylation of opiates using a home-made batch cell with low-cost porous glassy carbon electrodes. N-demethylation of opiates such as thebaine, codeine, morphine and oxycodone is a key step in the semi-synthesis of opioid medicines. The electrochemical N-demethylation using TEMPO as mediator enables the synthesis of noropiates, which is not possible with conventional Shono oxidation. Electrolysis was performed at a preparative scale in aqueous solvent at room

temperature in a single step, yielding the desired products in good isolated yields (up to 83%). Mechanistic studies suggest that the electrochemically generated oxoammonium species oxidizes the opiate to an iminium intermediate, which then hydrolyzes to the noropiate. The electrochemical reaction was also performed in a flow-cell without a supporting electrolyte and represents the first electrochemical N-demethylation of difficult opiates with an aminoxyl oxidant.


## 1. Introduction


The naturally occurring opiate alkaloids thebaine **1a**, oripavine **2a**, codeine **3a** and morphine **4a** (Figure 1,a) are used as starting compounds for the semi-synthesis of all opioid medicines in use today.<sup>[1]</sup> Naloxone **5a** is on the WHO list of essential medicines as the most important opioid antagonist and is used in the treatment of natural or synthetic opioid overdoses in an emergency. Naltrexone **5b** and nalmefene **5c** are used for the treatment of alcohol or opioid dependence. Nalbuphine **5d** and buprenorphine **6** are used as analgesic agents for moderate or severe pain.<sup>[2–4]</sup> These opiate therapeutic agents are typically synthesized from **1a** or **2a**, which are converted to oxycodone **7a** or oxymorphone **8a** through C14 hydroxylation and hydrogenation, before N-demethylation and subsequent functionalization.<sup>[1,3–6]</sup> However, **1a** is preferred over **2a** as starting compound due to its considerably higher natural abundance.<sup>[3,7]</sup> The most challenging step in the reaction sequence, from natural opiates to opiate-like therapeutics, is the selective N-demethylation of the highly functionalized

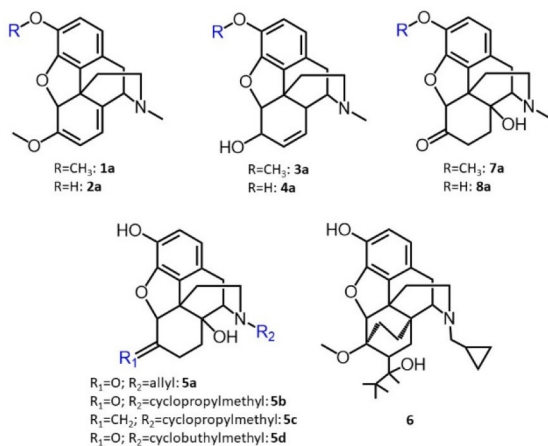
morphinan structure.<sup>[1–6,8–11]</sup> The classical route for selective N-demethylation involves the application of chloroformates<sup>[12,13]</sup> and cyanogen bromide<sup>[14–16]</sup> (von Braun reaction), forming carbamate and cyanamide intermediates, respectively, which subsequently hydrolyze to the desired secondary amine (Figure 1, b). Although these methods produce secondary amines in good yields, the requirement of highly toxic reagents at elevated temperature and the need to protect the phenol moiety in the morphinan structure limits their application.<sup>[3,4,10]</sup> Alternatively, the selective catalytic N-demethylation of opiate alkaloids can be achieved by the modified Polonovski reaction, which involves the formation of an N-oxide followed by its iron-based catalytic N-demethylation. This reaction requires strong oxidants such as H<sub>2</sub>O<sub>2</sub> or mCPBA as well as toxic solvents such as chloroform.<sup>[17–20]</sup> Over the past decade, various studies have demonstrated the palladium-catalyzed N-demethylation of opiates with oxygen as oxidant. An early study reported the N-demethylation/N-acylation of hydrocodone.<sup>[21]</sup> This method was later used for the synthesis of buprenorphine starting from thebaine<sup>[22]</sup> and the synthesis of naltrexone from an oxymorphone intermediate.<sup>[8]</sup> Recent Pd-catalyzed N-demethylation studies have focused on the aerobic continuous flow synthesis of noroxymorphone.<sup>[4,9,10]</sup> The reaction proceeded from morphine or oxymorphone intermediates via intramolecular N-acylation or oxazolidine formation. Pd-catalyzed methods generally produce the desired secondary amine in good yields. Alternatively, the oxazolidine intermediate can be obtained by aerobic oxidation of oxycodone using a photocatalyst<sup>[3]</sup> or electrochemistry<sup>[23]</sup> instead of the Pd-catalyst (Figure 1, c). However, these reactions require a second step for the hydrolysis of the oxazolidine structure.<sup>[3,4,9,10,23]</sup> Moreover, the electrochemical procedure is limited to opiates having an -OH or -Acyl group on carbon 14.<sup>[23]</sup> Further disadvantages are that these reactions require pure oxygen as terminal oxidant, which entails combustion and explosion hazards,<sup>[4,24]</sup> and proceed at elevated temperatures, using hazardous organic solvents and Pd-based

[a] A. A. Najmi, Prof. R. Bischoff, Dr. H. P. Permentier  
Department of Analytical Biochemistry  
Groningen Research Institute of Pharmacy  
University of Groningen  
A. Deusinglaan 1, 9713 AV Groningen, The Netherlands  
E-mail: h.p.permentier@rug.nl

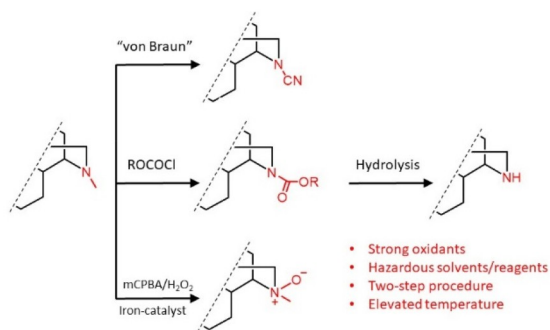
[b] M. F. Bhat, Prof. G. J. Poelarends  
Department of Chemical and Pharmaceutical Biology  
Groningen Research Institute of Pharmacy  
University of Groningen  
A. Deusinglaan 1, 9713 AV Groningen, The Netherlands

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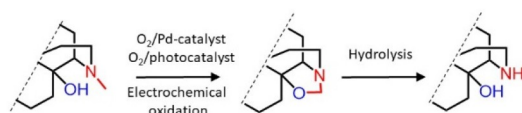
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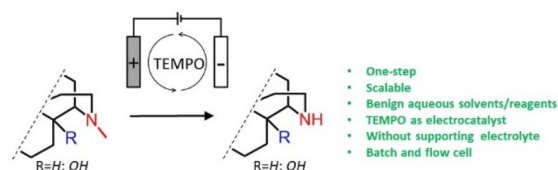
a) Opiate alkaloids and opiate-like medicines



b) Conventional N-demethylation strategies



c) N-demethylation via an oxazolidinone intermediate



d) This work

**Figure 1.** Opiate-like medicines and different N-demethylation strategies of opiates.

catalysts, which increase process costs due to the requirement of Pd removal to levels below 10 ppm.<sup>[2]</sup> Therefore, there is a clear need for new and better N-demethylation strategies to produce highly demanded opioid-like medicines.<sup>[25]</sup> Electro-organic synthesis is a versatile option for oxidation-reduction-based conversions and provides a powerful alternative to traditional organic chemistry methods as it applies less hazardous reagents, operates under milder reaction conditions and provides scalability and importantly sustainability.<sup>[26–30]</sup> Herein, we report a new TEMPO-mediated electrochemical N-demeth-

ylation strategy for the challenging class of opiate alkaloids that gives good product yields (47–83%) in a single step. The reaction proceeds at room temperature in a water/acetonitrile mixture and can be driven by photovoltaic elements converting light into electricity (Figure 1, d).

## 2. Materials and Methods

All chemicals and solvents were obtained from commercial vendors. All opiate compounds were obtained from the Groningen Research Institute of Pharmacy (GRIP) and the Interfaculty Mass Spectrometry Center (IMSC), University of Groningen, Groningen, The Netherlands. 100 PPI (pores per inch) porous glassy carbon (vitreous carbon) was purchased from Goodfellow Cambridge Ltd, UK. Electrochemical flow syntheses were performed in an electrochemical flow-cell containing 8 channels which were used in series. Each channel has a volume of about 88  $\mu\text{L}$  and 106 mm  $\times$  3 mm open area. Electrode dimensions were 110 mm  $\times$  45 mm. More information about the flow-cell is detailed elsewhere.<sup>[31–33]</sup> A syringe pump was used to pump the reaction solution through the flow-cell. An Autolab potentiostat (Metrohm AG) system controlled with NOVA software (Metrohm AG) was used to carry out galvanostatic and potentiostatic experiments. NMR spectra (<sup>1</sup>H and <sup>13</sup>C) were recorded on an Avance 500 spectrometer (Bruker). LC-MS analyses were performed using a C18 reversed phase chromatography column connected to a TSQ Quantum Ultra triple quadrupole mass spectrometer (Thermo Scientific) using an electrospray ionization (ESI) source. An Orbitrap Velos Pro (Thermo Scientific) with ESI source was used for high resolution mass spectrometry analysis. Chromatographic purifications were performed using either silica-gel for normal phase or C18 (XBridge, Waters) for reversed-phase chromatography. pH measurements were performed with pH indicator paper.

### 2.1. General Procedure for TEMPO-Mediated Electrochemical N-demethylation

For small scale experiments, 0.2 mmol of opiate (**1a**, **3a**, **7a**, **11a–15a**) were in HCl salt form and **10a** in HBr salt form), 0.2 mmol TEMPO and 1.6 mmol KNO<sub>3</sub> were dissolved in 3 mL acetonitrile and 1.3 mL water and then transferred to a glass tube cut to the proper length as reactor. Due to the limited solubility of **9a** in bitartrate salt form in the water/acetonitrile/KNO<sub>3</sub> system, **9a** was first isolated as the free amine and 0.2 mmol of **9a** and 0.2 mmol of HCl were dissolved in the same solvent system. The home-made electrochemical cell was inserted into the reactor. The top of the reactor was wrapped with Parafilm to minimize evaporation during the course of the reaction. For experiments running for more than 12 h in small scale experiments, 1–2 mL solvent was added to the reaction mixture after 12 h. For preparative experiments the concentration of all compounds was kept the same as for the small scale experiments, and 10 mL solvent was added to the system after 12 h to compensate for evaporation and uptake of

solvents by the electrodes. After 6–24 h, the electrodes were washed with methanol or ethanol to obtain the crude product, which was dried under reduced pressure. Upon the dissolution of dried crude product in methanol/dichloromethane (DCM) solution,  $\text{KNO}_3$  was precipitated (60–80%) and filtered out. The resulting solution was then dried under reduced pressure and purified over silica-gel or reversed phase column chromatography. After silica-gel chromatography, the eluate (MeOH/DCM) was dried under reduced pressure to obtain the product. In the case of reversed phase column purification, the eluate (water/acetonitrile) was either lyophilized directly to obtain the product or it was adjusted to pH = 11–12 with  $\text{NH}_4\text{OH}$  and then extracted with DCM. The organic layer was dried under reduced pressure to obtain the product. The isolated yield was calculated based on the weight of the final product.

## 2.2. Free-amine Isolation of Thebaine 1a

1 g of thebaine-HCl salt (white powder) is dissolved in 20 mL water/MeOH (3/1 v/v) and then basified with  $\text{NH}_4\text{OH}$  to pH = 11–12. The aqueous solution was extracted with DCM. The organic layer was dried under reduced pressure to obtain a yellow powder of **1a** as its free amine.

## 2.3. Chemical Reduction of TEMPO to TEMPOH

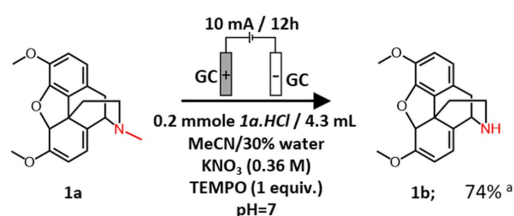
TEMPOH was synthesized according to a published method.<sup>[34]</sup> 1 g TEMPO, 1.87 g ascorbic acid, and 0.42 g NaOH were dissolved in 18 mL water and stirred vigorously. After 10–20 min, the orange color of the solution disappeared, and this was followed by formation of a white precipitate. The resulting

suspension was extracted with diethyl ether. The organic layer was washed with water and brine solution (saturated NaCl/water), dried over  $\text{Na}_2\text{SO}_4$  and then evaporated under reduced pressure to provide TEMPOH as an orange oil. The compound was stored at 4 °C.

## 3. Results and Discussion

Recently, we have successfully applied Shono oxidation for direct electrochemical N-demethylation of tropane alkaloids.<sup>[35]</sup> However, our effort to directly N-demethylate the important opiate alkaloid **1a** in the same manner or by using a recently reported electrochemical method,<sup>[23]</sup> under potentiostatic or galvanostatic reaction conditions using either **1a**·HCl or **1a** as free amine, did not lead to the desired N-demethylated compound **1b**. Therefore, we have developed a new indirect electrochemical procedure using TEMPO as electron mediator for the conversion of **1a** to **1b** (Figure 2). Importantly, the need for any expensive metal electrodes was avoided and a low-cost porous glassy carbon electrode was utilized as both anode and cathode (see supporting information, Figure SI 1–2).

To optimize the yield of the desired product **1b**, we tested different reaction conditions (Figure 2). A current of 10 mA was found to be optimal on a 0.2 mmol scale. Increasing the current to 20 mA or decreasing the current to 5 mA (while keeping the total amount of utilized electricity constant) had an unfavorable effect on the isolated yield. No reaction was observed in the absence of electricity or TEMPO, confirming the crucial role of TEMPO as electron mediator. Decreasing the amount of TEMPO to 0.5 equivalents led to a lower yield. Changing the supporting electrolyte from  $\text{KNO}_3$  to the more conventional  $\text{NaClO}_4$  did not lead to a large change in the yield. We therefore selected  $\text{KNO}_3$



entry	Deviation from above	Yield <sup>[b]</sup> [%]
1	No electricity	0
2	No TEMPO ( <b>1a</b> ·HCl or free amine)	0
3	MeCN/50% water	62
4	$\text{NaClO}_4$ instead of $\text{KNO}_3$	67
5	EtOH/50% water	58
6	MeOH/50% water	47
7	0.5 equiv. TEMPO	62
8	Free amine instead of HCl salt (pH = 9.5)	33
9	20 mA / 6 h	51
10	5 mA / 24 h	62

[a] average of four replicates using sets of glassy carbon electrodes. [b] isolated yield after reversed-phase chromatography (C18) purification based on the final weight of the obtained product **1b**.

**Figure 2.** Electrochemical N-demethylation of **1a** to **1b** under different conditions using a home-made batch cell.

as supporting electrolyte as it can be conveniently recovered (60–80%) due to its limited solubility in organic solvents. Switching from acetonitrile to other, more environmentally friendly solvents like ethanol or methanol, led to a lower yield. Finally, using **1a** in free amine form, which increased the pH of the solution to 9.5, decreased the yield considerably. The optimal reaction conditions for the electrochemical N-demethylation of **1a** to **1b** are summarized in the reaction scheme given in Figure 2.

Having established optimal reaction conditions, we next investigated the scale and scope of the TEMPO-mediated electrochemical N-demethylation of opiates (Figure 3). N-demethylation of **10a** was performed at 2-gram scale in the batch-cell with a 75% isolated product yield. A 1-gram scale synthesis of **1b** was performed in the same system with 65% yield. Although the reaction is practical under batch conditions, it takes a long time and requires  $\sim 60 \text{ F mole}^{-1}$  due to inefficient mass transport.<sup>[36,37]</sup> To overcome these limitations, we applied an 8-channel electrochemical flow-cell<sup>[31–33]</sup> using a planar graphite working electrode (Figure S14). The electrochemical N-demethylation of different opiates led to good product yields in this system even without adding  $\text{KNO}_3$  as supporting electrolyte. The electrochemical conversion of **10a** to **10b** using a 15 mL/h flow-rate and 60 mA applied current led to a comparable product yield (72%), while decreasing the required charge to  $3.4 \text{ F mole}^{-1}$ . Noroxycodone **7b**, which is considered an intermediate for the semi-synthesis of **5a** and **5b**,<sup>[4,6,10]</sup> was electrochemically synthesized from **7a** under the same reaction conditions with 47% yield. Electrochemical oxidation of morphine **4a** did not lead to quantitative formation of the N-demethylated product due to oxidation of the phenolic OH-group<sup>[23,38]</sup> leading to dimer forms as main products (Figure S15–7). When the OH groups in **4a** are protected by acetylation, as in **11a**, or when the phenol OH group in **4a** is replaced by a methoxy group, as in **3a**, the final product yield was comparable to that achieved with the other opiates.

To extend the usefulness of our synthetic approach, we performed the reaction on a 2-gram scale in a low-cost home-made system that is driven by a solar-powered cell. To this end, we replaced the potentiostat/galvanostat system with a low-cost DC-to-DC converter and connected it to a solar-panel-charged battery (see supporting information, Figure S12). Using this system, we obtained an isolated yield of **10b** that was comparable to the yield obtained under batch conditions. Upon connecting this system to the flow cell **14a** was converted to **14b** with a yield of 54%.

Next, we investigated the mechanism of the TEMPO-mediated electrochemical N-demethylation reaction (Figure 4). LC-MS analysis of the electrochemical N-demethylation of **1a** in the presence of TEMPO during the course of the reaction showed the formation of TEMPOH ( $m/z$  of 158.1, see Figure S18), which supports the two-electron reduction of the produced oxoammonium species upon electrochemical oxidation of TEMPO at the electrode,<sup>[39]</sup> while oxidizing **1a** to the iminium intermediate via a two-electron oxidation. The iminium intermediate then hydrolyzes to produce **1b** and formaldehyde. The generated TEMPOH oxidizes back to the oxoammonium species

at the anode allowing further oxidation of **1a**. This mechanism is similar to the Shono oxidation<sup>[40–42]</sup> which follows a two-electron/one-proton electrochemical oxidation to form an iminium intermediate in order to activate C–H bonds in the neighborhood of a nitrogen atom.<sup>[43–45]</sup> Several control experiments were performed to support the proposed mechanistic pathway. Electrochemical oxidation of TEMPO itself in the same solvent system in the absence of any opiates did not lead to the formation of TEMPOH. In order to perform a control experiment in which the reaction is initiated with TEMPOH instead of TEMPO, TEMPOH was first synthesized by reduction of TEMPO using sodium ascorbate. As expected, the electrochemical N-demethylation of **1a** to **1b** was successfully carried out using TEMPOH instead of TEMPO as starting mediator. A control experiment of TEMPOH/**1a** in the absence of electricity did not lead to any product, as expected. In another experiment, the anode and cathode were separated using a salt-bridge (gelatin/saturated- $\text{KNO}_3$ -water). In this condition, anodic and cathodic reaction solutions are not mixed with each other while maintaining conductivity through the salt-bridge allowing the study of the oxidation and reduction reactions individually (see supporting information, Figure S13). LC-MS analysis of the electrochemical oxidation of **1a** in the divided electrochemical cell clearly showed the presence of **1b** and TEMPOH in the anode compartment, supporting the proposed mechanism (see supporting information, Figure S19). Moreover, the formaldehyde produced at the anode upon hydrolysis of the hypothesized iminium intermediate was detected using a derivatization with acetylacetone and ammonia forming 3,5-diacetyl-1,4-dihydroxylutidine ( $m/z$  of 194.1), which was detected by LC-MS.<sup>[35,46,47]</sup> As expected, there was no formaldehyde detected in the cathode compartment (see supporting information, Figure S110).

## 4. Conclusions

In summary, we describe for the first time a TEMPO-mediated electrochemical N-demethylation of opiates that is conveniently scalable without the need for a supporting electrolyte or a potentiostat/galvanostat using a solar-powered battery to produce noropiates. This indirect TEMPO-mediated electrochemical approach allows the N-demethylation of several opiates, which is not possible with direct electrochemical oxidation procedures. The practicality of the new methodology was shown by using a home-made batch cell to synthesize different noropiates in gram scale. Although the reaction is feasible in batch conditions, the reaction takes a rather long time (with consumption of more charge) due to a less efficient mass transport. Alternatively, the reaction can be performed in an electrochemical flow-cell with good product yields and a 15-fold more efficient use of electricity. The mechanistic studies showed that the electrochemical N-demethylation of opiates starts with a single-electron oxidation of TEMPO to an oxoammonium species which triggers a two-electron oxidation of the opiates to a presumed iminium intermediate, which then hydrolyzes to afford the desired noropiates. These results show

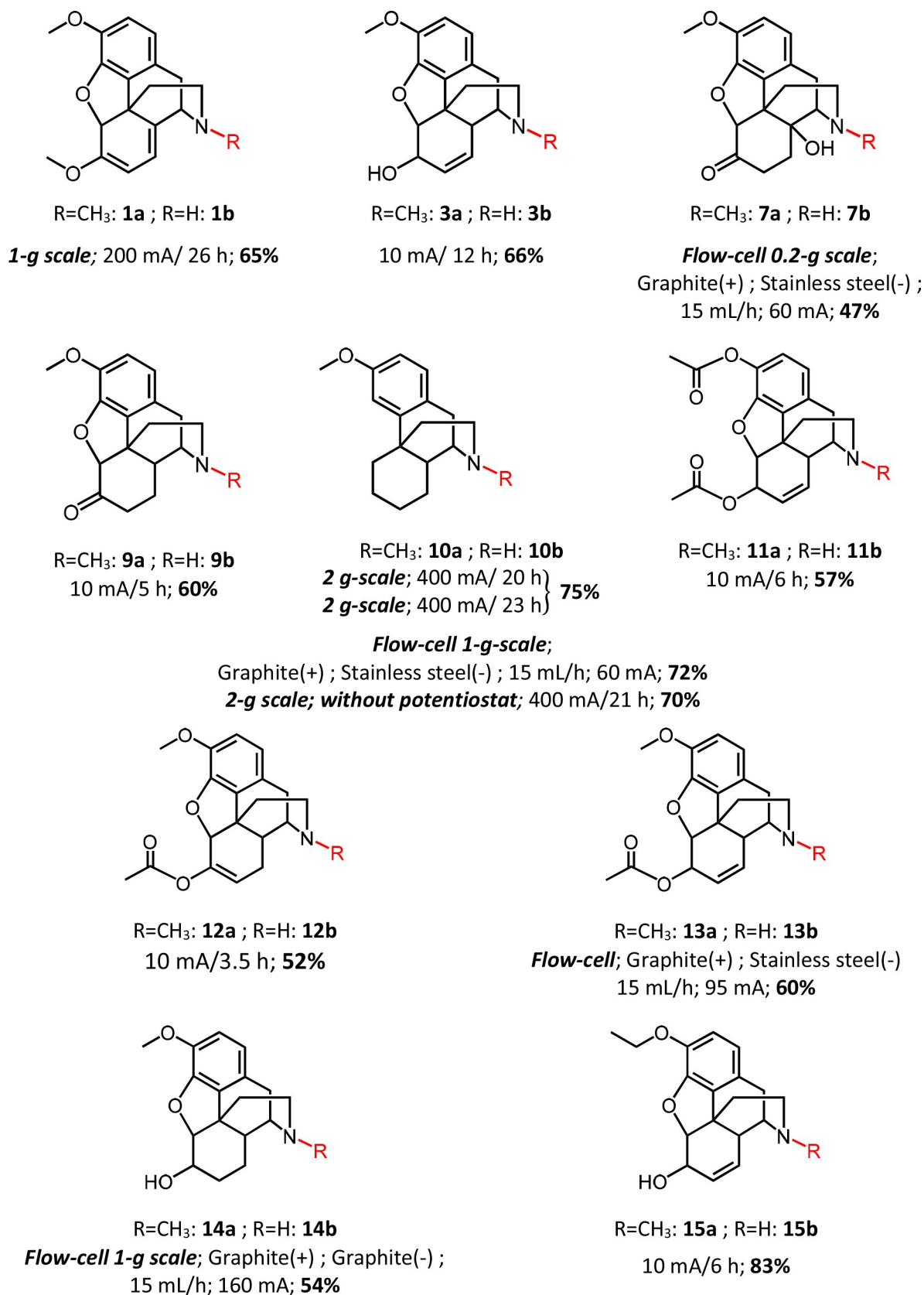
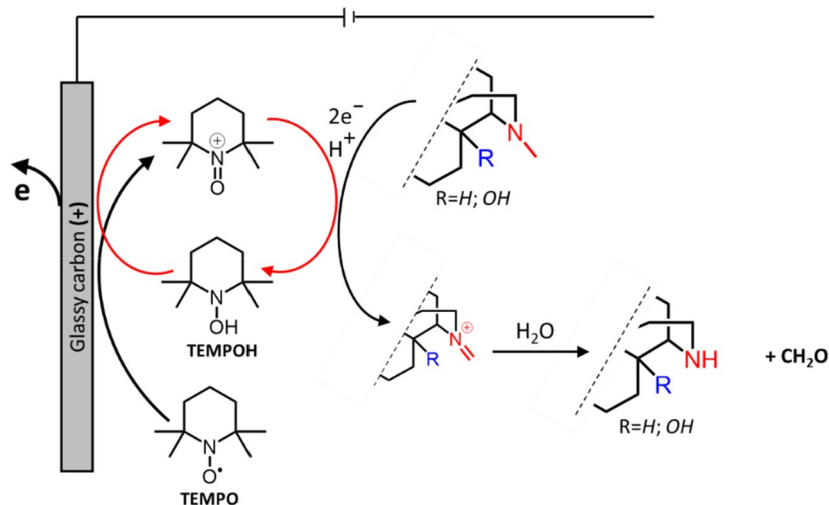


Figure 3. Scale and scope of the TEMPO-mediated electrochemical N-demethylation reaction.



**Figure 4.** Plausible mechanism for TEMPO-mediated electrochemical N-demethylation of opiates.

the potential of TEMPO-mediated electrochemical oxidations for the synthesis of noropiates and lay the groundwork for subsequent studies towards the development of new mediated-electrosynthesis methods to decrease the consumption of electrocatalyst and to improve the efficiency of the reaction.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** electrocatalysis · flow cell · N-demethylation · opiates · TEMPO

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