TEMPO–Me: An Electrochemically Activated Methylating Agent

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ABSTRACT: Bench- and air-stable 1-methoxy-2,2,6,6-tetramethylpiperidine (TEMPO–Me) is relatively unreactive at ambient temperature in the absence of an electrochemical stimulus. In this report, we demonstrate that the one-electron electrochemical oxidation of TEMPO–Me produces a powerful electrophilic methylating agent *in situ*. Our computational and experimental studies are consistent with methylation proceeding *via* a S_N2 mechanism, with a strength comparable to the trimethyloxonium cation. A protocol is developed for the electrochemical methylation of aromatic acids using TEMPO–Me.

INTRODUCTION

Methylation is a ubiquitous, fundamental process in biological and chemical systems.[1-2] In biology, methylation can be achieved through enzymatic methyl transfers often involving *S*-adenosyl methionine.[3] In chemical synthesis, both electrophilic and nucleophilic (including radical) sources of the methyl group are commonly deployed in a variety of contexts.[1, 4-6] Electrophilic methylation is typically achieved using a reagent bearing a highly stabilized leaving group.[7] Consequently, many established methylating agents, such as iodomethane, dimethyl sulfate, methyl triflate or diazomethane (or its derivatives) exhibit acute toxicity. Some of these reagents are also particularly volatile and/or potentially explosive.[8] Safer and "greener" alternatives have arisen, such as dimethyl carbonate, but these are often less reactive.[9]

The development of new compounds that can serve as reactive, *in-situ*-generated methylating agents offers many advantages. Indeed, various reagents such as *N,N*-dimethylformamide dimethyl acetal or trimethyl orthoacetate have been used in this capacity.[10-11] Safer strategies have also been developed in which powerful alkylating species such as diazomethane are prepared and reacted *in situ*,[12-13] thus eliminating the need to isolate and handle hazardous reagents. In these cases, chemical reagents and/or inputs of thermal energy provide active methylating species in solution. Identifying alternative strategies that can provide access to highly reactive methylating agents from latent, relatively non-toxic precursors under mild conditions remains of fundamental and practical interest.

Alkoxyamines feature heat-labile C–O bonds, but are typically stable at ambient temperature.[14] At elevated temperatures, thermally-induced homolytic bond cleavage of certain alkoxyamines can provide a persistent nitroxide and carbon-centered radical (Scheme 1). This property of alkoxyamines has led to their prolific use in polymer chemistry and materials science.[15]

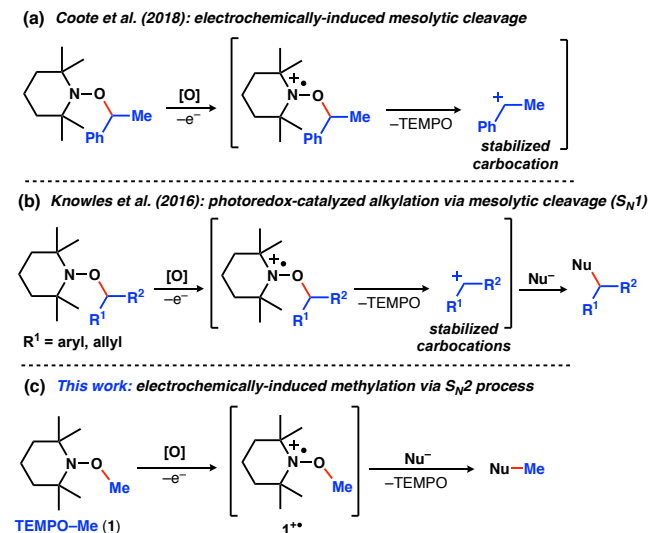**Scheme 1. Conventional homolytic reactivity of alkoxyamines.**
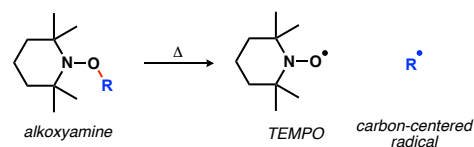
In 2018, we demonstrated that an electrochemically-promoted one-electron oxidation of a styrene-derived alkoxyamine results in rapid and irreversible mesolytic bond cleavage, producing a stable nitroxide radical and a carbocation at ambient temperature, rather than a carbon-centered radical (Scheme 2a).[16] Similar approaches for the generation of stabilized (e.g., benzylic) cations have also been reported using photoredox catalysis (Scheme 2b),[17-18] or conventional single-electron chemical oxidants, and have been used for alkylation procedures operating *via* S_N1 reactivity.[19] This reveals that alkoxyamines capable of providing stabilized carbocation intermediates are prone to spontaneous fragmentation under oxidative conditions.[17-20] However, the formation of unstabilized carbocations from alkoxyamines *via* mesolytic cleavage is more challenging due to the higher C–O bond dissociation energy of the alkoxyamine radical cations.[17, 21-22]

We have previously shown that the oxidized form of 1-methoxy-2,2,6,6-tetramethylpiperidine (TEMPO–Me, **1**) is resistant to direct mesolytic cleavage.[22] However, in this work we demonstrate that the electrophilicity of this radical cation can still be harnessed in the form of S_N2 reactivity. Ultimately, we define a new strategy for the *in situ* electrochemical generation of an active methylating agent (**1$^{+•}$**) from latent, relatively benign TEMPO-Me (Scheme 2c). In this process, the use of electrochemistry obviates the need for transition metal catalysts or stoichiometric chemical oxidants.

Scheme 2. (a) Electrochemically-promoted mesolytic bond cleavage of alkoxyamines. (b) Photoredox-catalyzed alkylation *via* mesolytic bond cleavage of

alkoxyamines. (c) Electrochemical methylation employing TEMPO–Me.

(a) *Coote et al. (2018): electrochemically-induced mesolytic cleavage*

(b) *Knowles et al. (2016): photoredox-catalyzed alkylation via mesolytic cleavage (S$_N$1)*

R^1 = aryl, allyl

(c) *This work: electrochemically-induced methylation via S$_N$2 process*

TEMPO–Me (1)   1$^{+•}$

RESULTS AND DISCUSSION

Synthesis of TEMPO-Me. In order to explore the utility of TEMPO–Me (**1**) as a potential methylating agent, a simple and efficient synthesis was essential. While this alkoxyamine has often been identified as a product in radical trapping experiments, there are few reports of its isolation and extensive characterization.[23-26] Using Fenton-type chemistry we were able to achieve a high-yielding multi-gram synthesis of **1** from TEMPO (Scheme 3).[27] We found that the product was stable to flash column chromatography and no degradation was observed after storage under air, at ambient temperature and in the presence of natural light over *ca.* 6 months.

Scheme 3. Synthesis of TEMPO–Me (1).

FeSO$_4$.7H$_2$O
H$_2$O$_2$, DMSO
94% yield
5 gram scale

TEMPO

TEMPO–Me (1)
bench & air-stable
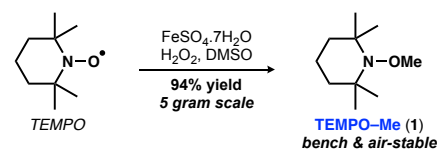
Cyclic Voltammetry Studies. When analyzed by cyclic voltammetry, TEMPO-Me (**1**) displayed a reversible redox couple at a potential of +1.22 V *vs.* Ag/AgCl in MeCN, consistent with the formation of the radical cation **1**$^{+•}$ in the absence of any observable C–O bond cleavage (Figure 1a). However, when pyridine (4 equiv) was added, the oxidation of TEMPO–Me (**1**) was found to be irreversible, indicating a subsequent chemical transformation (Figure 1b). Specifically, signals consistent with the concomitant production of TEMPO and an *N*-methylpyridinium species under these conditions were evident after the first anodic scan and persisted in subsequent scans, typical of an EC$_{ir-rev}$E mechanism of C–O cleavage.[16] The assignment of these additional signals was supported by comparison of the cyclic voltammograms of *N*-methylpyridinium iodide[28] (Figure 1c) and

TEMPO (Figure 1d) measured separately under identical conditions. When taken together, these data are consistent with a bimolecular substitution reaction between the electrochemically-formed radical cation **1**$^{+•}$ and a nucleophile to deliver a methylated product (Figure 1e). Certainly, the persistence of radical cation **1**$^{+•}$ in solution (in the absence of a nucleophile) strongly suggests that that nucleophilic substitution does not proceed *via* a S$_N$1 mechanism.
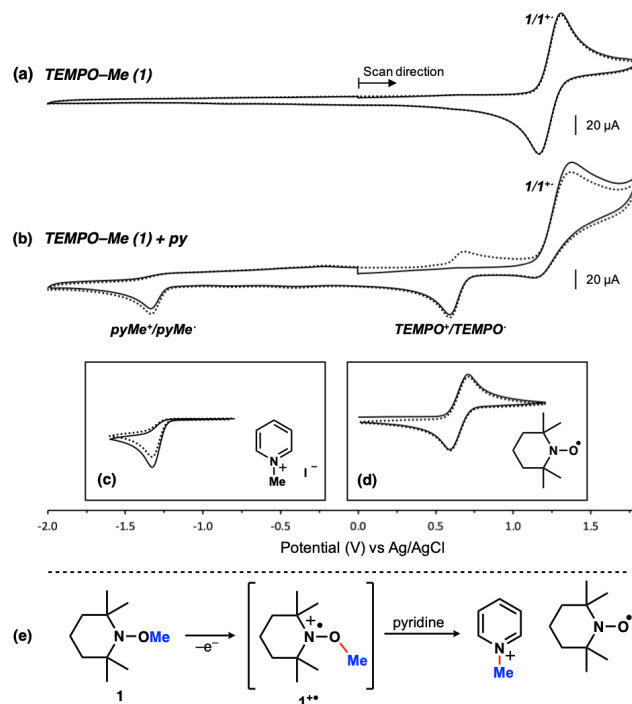

Figure 1. Cyclic voltammogram of a solution of substrate (2 mM) and Bu$_4$NClO$_4$ (0.1 M) in MeCN; Ag/AgCl reference electrode. Scan rate: 500 mV.s^{-1}. *Solid line* = scan 1, *dotted line* = scan 2. (**a**) TEMPO–Me (**1**). (**b**) TEMPO–Me + pyridine (4 equiv). (**c**) *N*-methylpyridinium iodide. (**d**) TEMPO. (**e**) Oxidation of TEMPO–Me (**1**) and subsequent reaction with pyridine.

Theoretical Mechanistic Studies. Recently, we used theory and experiment to study the effect of solvent and electrolyte on the C–O fragmentation of another alkoxyamine that also lacks strong stabilizing functional groups, 1-*iso*-propoxy-2,2,6,6-tetramethylpiperidine (TEMPO–*i*Pr).[29] We found that cleavage could be promoted to varying extents by some coordinating solvents (THF, MeNO$_2$, MeCN) and electrolyte anions (NO$_3^-$, HSO$_4^-$, TfO$^-$, ClO$_4^-$, BF$_4^-$), or inhibited under non-coordinating conditions (Bu$_4$NPF$_6$ in CH$_2$Cl$_2$). Theoretical calculations identified S$_N$2 transition states for the cleavage of TEMPO–*i*Pr by coordinating species, with rate coefficients consistent with those fitted to the experimental cyclic voltammograms. A similar mode of reactivity can be envisaged between TEMPO–Me and pyridine. This is consistent with the fact that, while the use of various coordinating solvents or anions made no observable difference to the voltammogram of **1**, a more nucleophilic additive (pyridine) was able to cause reactivity.

With this in mind, we examined the S$_N$2 transition state energies of a selection of common methylating agents with pyridine as a reference nucleophile, which allowed us to compare the respective methylation strengths of these molecules with

methoxyamine radical cation $1^{+\bullet}$ (Table 1). We found that $1^{+\bullet}$ gave lower activation energies and more favorable overall reaction energies than methyl triflate and was comparable to the trimethyloxonium cation – both generally recognized as powerful electrophiles. This suggested that species $1^{+\bullet}$ could serve as a potent methylating agent.

Table 1. Comparison of (TEMPO–Me)$^{+\bullet}$ ($1^{+\bullet}$) with common methylating agents, using pyridine as a reference nucleophile.[a]

Electrophile	$\Delta G^{\ddagger}$	ΔG_{rxn}
MeOTf	73.2	−119.6
Me$_3$O$^+$	67.7	−121.3
(TEMPO–Me)$^{+\bullet}$	66.5	−124.9
MeN$_2^+$	31.5	−254.7

[a] in kJ.mol^{-1}, calculated using G3(MP2,CC)(+)//M06-2X/6-31+G(d,p).

Reaction Optimization. As a case study of the feasibility of **1** as a methylating agent in a synthetically useful setting on a preparative scale, we then investigated the electrochemical methylation of carboxylic acids to produce their corresponding methyl esters. In cyclic voltammetry experiments, benzoic acid was insufficiently nucleophilic to react with $1^{+\bullet}$ to an appreciable extent. In contrast, the benzoate anion caused C–O fragmentation to produce TEMPO in an analogous fashion to the aforementioned reaction with pyridine (see Supporting Information for full voltammograms).

When these findings were applied on a preparative scale (0.5 mmol) using the standardized IKA Electrasyn 2.0 cell (10 mL) and graphite electrodes, it was found that benzoic acid could be converted to methyl benzoate in the presence of either potassium carbonate or cesium carbonate under a constant current of 10 mA, albeit in low isolated yields (Table 2, entries 1 and 2). In the presence of these heterogeneous bases, significant deposition on the cathode was observed which, if the cell polarity was not regularly alternated, completely inhibited the reaction. In contrast, the use of the homogeneous, non-nucleophilic base, 2,6-di-*tert*-butyl-pyridine, increased the yield and did not require alternating cell polarity (entry 3). Cyclic voltammetry studies suggest that this base does not react with $1^{+\bullet}$ directly, however, less hindered pyridine bases such as 2,6-lutidine were found to be competitive nucleophiles (see Supporting Information).

The use of acetonitrile as solvent afforded better results than dichloromethane (entry 4), while THF and DMSO both failed to give any isolable product, as much higher solution resistances were observed (entries 5 and 6). Changing the electrolyte from Bu$_4$NBF$_4$ to either Bu$_4$NPF$_6$ or Bu$_4$NClO$_4$ gave enhanced yields, with the latter providing a 51% yield (entries 7 and 8). The yield of methyl benzoate was essentially

Table 2. Electrochemical methylation of benzoic acid using TEMPO–Me: Influence of reaction parameters.[a]
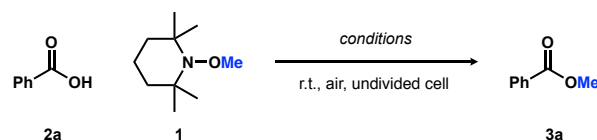

Entry	Electrolyte	Solvent	Base (eq.)		Electrolytic Conditions	F.mol^{-1}	Isolated Yield (%)[b]
1	Bu$_4$NBF$_4$	MeCN	Cs$_2$CO$_3$	(1.1)	10 mA	12.2	0 (13)[c]
2	Bu$_4$NBF$_4$	MeCN	K$_2$CO$_3$	(1.1)	10 mA	12.2	0 (21)[c]
3	Bu$_4$NBF$_4$	MeCN	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	(1.1)	10 mA	12.2	37
4	Bu$_4$NBF$_4$	CH$_2$Cl$_2$	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	(1.1)	10 mA	12.2	22
5	Bu$_4$NBF$_4$	THF	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	(1.1)	10 mA	12.2	0
6	Bu$_4$NBF$_4$	DMSO	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	(1.1)	10 mA	12.2	0
7	**Bu$_4$NPF$_6$**	MeCN	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	(1.1)	10 mA	12.2	44
8	**Bu$_4$NClO$_4$**	MeCN	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	(1.1)	10 mA	12.2	51
9	Bu$_4$NClO$_4$	MeCN	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	**(0.25)**	10 mA	12.2	50
10	Bu$_4$NClO$_4$	MeCN	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	**(0.10)**	10 mA	12.2	51
11	Bu$_4$NClO$_4$	MeCN	None	-	10 mA	12.2	22
12	Bu$_4$NClO$_4$	MeCN	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	(0.10)	**5 mA**	**6.1**	46
13	Bu$_4$NClO$_4$	MeCN	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	(0.10)	**15 mA**	**18.3**	25
14	Bu$_4$NClO$_4$	MeCN	2,6-(*t*-Bu)$_2$C$_5$H$_3$N	(0.10)	10 mA	6.7	91[d]

[a] Reactions consisted of **2a** (0.5 mmol), **1** (0.55 mmol, 1.1 eq.), and base (stated equivalents) in an electrolyte solution (10 mL; 0.1 M) electrolyzed in a 10 mL undivided cell at room temperature open to air for 18 h using an IKA Electrasyn 2.0 and two graphite electrodes, unless otherwise specified. [b] Yield with respect to **2a**. [c] Yield obtained when the cell polarity was reversed every 10 minutes. [d] 2.0 eq. of **1**.

unchanged when the loading of 2,6-di-*tert*-butyl-pyridine was lowered to catalytic levels (entries 9 and 10). There have been reports of the electrochemical reduction of protonated pyridine species for the production of H_2,[30-31] suggesting that a reduction process at the cathode may play a role to regenerate the base in our methylation protocol. In the absence of base, the reaction proceeded in greatly reduced yield (entry 11).

As expected, variations in the electrolytic conditions had a pronounced effect on the efficiency of the reaction. Employing a lower 5 mA current decreased the reaction rate and yield (entry 12), while at 15 mA, an increase in decomposition greatly reduced efficiency (entry 13). Ultimately, using 2 equivalents of **1** was optimal, and furnished ester **3a** in 91% yield (entry 14). Alternatively, under potentiostatic operation and slightly different reaction conditions, a good yield of methyl benzoate could still be obtained in 8 h (Scheme 4b).

Scheme 4. Conventional chemical oxidants or photoredox catalysis do not facilitate the methylation of benzoic acid.
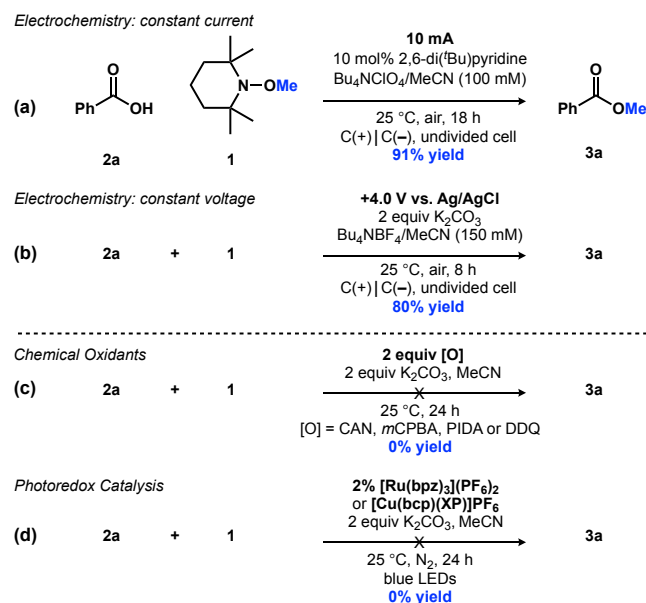
Electrochemistry was crucial to facilitating the methylation of benzoic acid (Scheme 4a, b). Chemical oxidants such as ceric ammonium nitrate (CAN),[19] *m*-chloroperbenzoic acid (*m*CPBA),[27] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), and (diacetoxyiodo)benzene (PIDA) proved to be ineffective in enabling this transformation (Scheme 4c). In each case, compound **1** was essentially unreacted and methyl benzoate was not formed. We were also unable to promote this reaction via photoredox catalysis. For example, employing either [Ru(2,2'-bipyrazyl)$_3$]$^{2+}$ (E_{ox} = +1.58 V vs. Ag/AgCl in MeCN) or [Cu(bathocuproine)(xantphos)]$^+$, (E_{ox} = +1.44 V vs. Ag/AgCl in MeCN) did not provide product **3a** (Scheme 4d).[17, 32] This is consistent with previous observations noting the difficulty in generating less stabilized carbocations from alkoxyamines *via* photoredox catalysis.[17] Thus, these results highlight the unique capacity for electrochemistry to promote reactivity that is otherwise unattainable.

Reaction Scope. Following this, we explored the scope of the reaction with a range of electronically- and sterically-varied carboxylic acids (Figure 2). When the optimal conditions were used (Table 2, entry 14), methyl *p*-toluate (**3b**) and methyl 4-fluorobenzoate (**3c**) were isolated in 97% and 60% yields, respectively. 4-Fluorobenzoic acid could be prepared in a higher yield using the alternative potentiostatic procedure (as in Scheme 4b). 4-(*tert*-Butyl)benzoic acid (**2d**) was also methylated in good yield, in addition to the *ortho*-substituted substrate 2-phenylbenzoic acid (**2e**). The heteroaromatic acid, thiophene-2-carboxylic acid was efficiently converted into ester **3f**, while monoethyl phthalate and 2-naphthoic acid also provided respective products **3g** and **3h**.

All of these reactions could be conducted in an undivided cell, however, for substrates featuring functional groups more susceptible to electroreduction, the methylation procedure was performed in a simple divided cell setup, detailed in the Supporting Information, Appendix S3. For instance, *p*-nitrobenzoic acid gave a complex mixture of products when reacted in an undivided cell. This presumably derived from the reduction of the nitro group. However, when reacted in a divided cell, this compound could be methylated to afford ester **3i**. In these cases, cesium carbonate was found to be the most efficient base and the catalytic activity of 2,6-di-*tert*-butyl-pyridine was inhibited. Under these conditions, ketone-containing substrate **2j** was compatible and *trans*-cinnamic and phenylpropiolic acids could be methylated to give **3k** and **3l**, respectively.
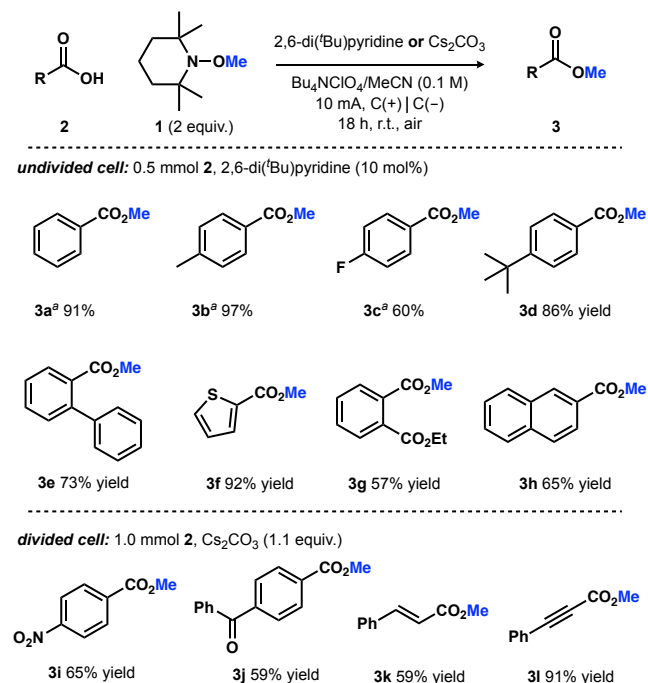

Figure 2. Electrochemical methylation of carboxylic acids employing TEMPO–Me. [a] These reactions were also conducted under the alternative potentiostatic conditions: Scheme 4b; 1 mmol of **2**. Isolated yields of **3a**, **3b**, and **3c** were 80%, 81% and 83% respectively.

While high yields were obtained in specific cases, we envisage that more refined divided cell conditions could increase the efficiency and scope of this process to an even greater extent. Similarly, the utilization of electrochemical flow systems would undoubtedly allow fine-tuning and optimization of these transformations,[33-34] this is however beyond the scope of this

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report. Further improvements may also lie in the development of an analogue of alkoxyamine **1** that is more susceptible to electrochemical oxidation. This may increase the scope of this methylation process to a wider range of nucleophiles which are currently challenging when competitive oxidation occurs. In this regard, recent findings will be instructive.[35-36] Through structural changes it may also be beneficial to adjust the difference in the reduction potential of the alkoxyamine and the corresponding nitroxide, as our investigations revealed that the addition of excess TEMPO inhibited the methylation (see Appendix S2).

Deuterium Labelling. As discussed earlier, mechanistic studies on closely related systems provide further evidence that supports the operation of a S_N2 mechanism in this methylation process.[29] However, the oxidative cleavage of *N*-methoxyamines mediated by *m*CPBA in dichloromethane has been reported.[27] The authors propose that this transformation proceeds *via* a Cope-type elimination mechanism in which the methyl substituent is liberated as formaldehyde. In order to exclude the possibility that the reaction proceeds *via* the deprotonation of radical cation **1⁺•** to afford a transient carbene species (or formaldehyde), the deuterated analogue TEMPO–CD$_3$ (***d*$_3$–1**, >99% D incorporation) was prepared from *d*$_6$-DMSO. When ***d*$_3$–1** was reacted with *p*-nitrobenzoic acid (**2i**) under the standard conditions, no evidence of H/D exchange was observed in benzoate ***d*$_3$–3i** as judged by mass spectrometry and NMR spectroscopy (Scheme 5). Beyond the mechanistic implications of this experiment, this also demonstrates the capacity of this chemistry to facilitate *d*$_3$-methylation with isotopic retention.

Scheme 5. Selective *d*$_3$-methylation with TEMPO–CD$_3$.
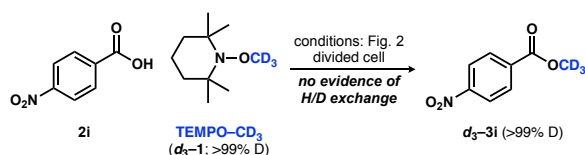
CONCLUSION

In summary, we have demonstrated that air- and bench-stable TEMPO–Me (**1**), which can be prepared in a single step on a multigram scale, represents a novel latent methylating agent. Specifically, we have determined that a one-electron electrochemical oxidation allows an active electrophile (radical cation **1⁺•**) to be generated and reacted *in situ*. These intermediates were previously thought to be unreactive in alkylation chemistry, however, we have demonstrated that resistance to mesolytic cleavage is not necessarily a hindrance in this regard. We have confirmed the viability of this novel electrochemically-electrophilic methylation for a range of carboxylic acids. Our computational and experimental studies are consistent with this novel transformation proceeding *via* a S_N2 mechanism involving attack of a nucleophile to oxidized TEMPO–Me derivative **1⁺•**. The capacity to generate this or related reactive intermediates under mild conditions by simply using an electrochemical stimulus presents exciting possibilities and opportunities in synthesis. Additional studies exploring the electrochemical activation of alkoxyamines and related compounds within the context of chemical alkylation are underway.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

REFERENCES

1. Chen, Y., Recent Advances in Methylation: A Guide for Selecting Methylation Reagents. *Chem. - Eur. J.* **2019**, *25*, 3405-3439.
2. Luo, M., Chemical and Biochemical Perspectives of Protein Lysine Methylation. *Chem. Rev.* **2018**, *118*, 6656-6705.
3. Takusagawa, F.; Kamitori, S.; Misaki, S.; Markham, G. D., Crystal Structure of *S*-Adenosylmethionine Synthetase. *J. Biol. Chem.* **1996**, *271*, 136-147.
4. Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M., The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215-5246.
5. Schönherr, H.; Cernak, T., Profound Methyl Effects in Drug Discovery and a Call for New C-H Methylation Reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256-12267.
6. Lamoureux, G.; Agüero, C., A Comparison of Several Modern Alkylating Agents. *ARKIVOC (Gainesville, FL, U. S.)* **2009**, *1*, 251-264.
7. Carey, F. A.; Sundberg, R. J., *Advanced Organic Chemistry 5th Ed.* Springer: New York, 2007.
8. Sammakia, T., Diazomethane. In *Encyclopedia of Reagents for Organic Synthesis*, Wiley: 2001.
9. Tundo, P.; Selva, M., The Chemistry of Dimethyl Carbonate. *Acc. Chem. Res.* **2002**, *35*, 706-716.
10. Stanovnik, B.; Tisler, M.; Hribar, A.; Barlin, G. B.; Brown, D. J., Methylation of Heterocyclic Compounds Containing NH, SH and/or OH Groups by means of *N,N*-Dimethylformamide Dimethyl Acetal. *Aust. J. Chem.* **1981**, *34*, 1729-1738.
11. Trujillo, J. I.; Gopalan, A. S., Facile Esterification of Sulfonic Acids and Carboxylic Acids with Triethylorthoacetate. *Tetrahedron Lett.* **1993**, *34*, 7355-7358.
12. Morandi, B.; Carreira, E. M., Iron-Catalyzed Cyclopropanation in 6 M KOH with in Situ Generation of Diazomethane. *Science* **2012**, *335*, 1471-1474.
13. Dallinger, D.; Kappe, C. O., Lab-Scale Production of Anhydrous Diazomethane using Membrane Separation Technology. *Nat. Protoc.* **2017**, *12*, 2138-2147.
14. Nesvadba, P., N-Alkoxyamines: Synthesis, Properties, and Applications in Polymer Chemistry, Organic Synthesis, and Materials Science. *CHIMIA International Journal for Chemistry* **2006**, *60*, 832-840.

15. Blinco, J. P.; Bottle, S. E.; Fairfull-Smith, K. E.; Simpson, E.; Thomas, K., Chapter 3 Synthesis of Nitroxides and Alkoxyamines. In *Nitroxide Mediated Polymerization: From Fundamentals to Applications in Materials Science*, The Royal Society of Chemistry: 2016; pp 114-152.

16. Zhang, L.; Laborda, E.; Darwish, N.; Noble, B. B.; Tyrell, J. H.; Pluczyk, S.; Le Brun, A. P.; Wallace, G. G.; Gonzalez, J.; Coote, M. L.; Ciampi, S., Electrochemical and Electrostatic Cleavage of Alkoxyamines. *J. Am. Chem. Soc.* **2018,** *140*, 766-774.

17. Zhu, Q.; Gentry, E. C.; Knowles, R. R., Catalytic Carbocation Generation Enabled by the Mesolytic Cleavage of Alkoxyamine Radical Cations. *Angew. Chem., Int. Ed.* **2016,** *55*, 9969-9973.

18. Gentry, E. C.; Rono, L. J.; Hale, M. E.; Matsuura, R.; Knowles, R. R., Enantioselective Synthesis of Pyrroloindolines via Noncovalent Stabilization of Indole Radical Cations and Applications to the Synthesis of Alkaloid Natural Products. *J. Am. Chem. Soc.* **2018,** *140*, 3394-3402.

19. O'Brya, G.; Braslau, R., Terminal Functionalization of Polymers via Single Electron Oxidation of *N*-Alkoxyamines. *Macromolecules* **2006,** *39*, 9010-9017.

20. Zhang, L.; Espíndola, B. R.; Noble, B. B.; Gonçales, R. V.; Wallace, G. G.; Darwish, N.; Coote, L. M.; Ciampi, S., Switchable Interfaces: Redox Monolayers on Si(100) by Electrochemical Trapping of Alcohol Nucleophiles. *Surfaces* **2018,** *1*, 3-11.

21. Marsal, P.; Roche, M.; Tordo, P.; de Sainte Claire, P., Thermal Stability of O–H and O–Alkyl Bonds in *N*-Alkoxyamines. A Density Functional Theory Approach. *J. Phys. Chem. A* **1999,** *103*, 2899-2905.

22. Hammill, C. L.; Noble, B. B.; Norcott, P. L.; Ciampi, S.; Coote, M. L., Effect of Chemical Structure on the Electrochemical Cleavage of Alkoxyamines. *J. Phys. Chem. C* **2019,** *123*, 5273-5281.

23. Wang, Y.; Zhang, L.; Yang, Y.; Zhang, P.; Du, Z.; Wang, C., Alkene Oxyalkylation Enabled by Merging Rhenium Catalysis with Hypervalent Iodine(III) Reagents via Decarboxylation. *J. Am. Chem. Soc.* **2013,** *135*, 18048-18051.

24. Wu, X.; Riedel, J.; Dong, V. M., Transforming Olefins into γ,δ-Unsaturated Nitriles through Copper Catalysis. *Angew. Chem., Int. Ed.* **2017,** *56*, 11589-11593.

25. Tang, F.; Qu, F.; Khusnutdinova, J. R.; Rath, N. P.; Mirica, L. M., Structural and Reactivity Comparison of Analogous Organometallic Pd(III) and Pd(IV) Complexes. *Dalton Trans.* **2012,** *41*, 14046-14050.

26. Schultz, J. W.; Fuchigami, K.; Zheng, B.; Rath, N. P.; Mirica, L. M., Isolated Organometallic Nickel(III) and Nickel(IV) Complexes Relevant to Carbon–Carbon Bond Formation Reactions. *J. Am. Chem. Soc.* **2016,** *138*, 12928-12934.

27. Chalmers, B. A.; Morris, J. C.; Fairfull-Smith, K. E.; Grainger, R. S.; Bottle, S. E., A Novel Protecting Group Methodology for Syntheses using Nitroxides. *Chem. Commun.* **2013,** *49*, 10382-10384.

28. Lebègue, E.; Agullo, J.; Bélanger, D., Electrochemical Behavior of Pyridinium and *N*-Methyl Pyridinium Cations in Aqueous Electrolytes for CO_2 Reduction. *ChemSusChem* **2018,** *11*, 219-228.

29. Noble, B. B.; Norcott, P. L.; Hammill, C. L.; Ciampi, S.; Coote, M. L., Mechanism of Oxidative Alkoxyamine Cleavage: The Surprising Role of the Solvent and Supporting Electrolyte. *J. Phys. Chem. C* **2019,** *123*, 10300-10305.

30. Keith, J. A.; Carter, E. A., Electrochemical Reactivities of Pyridinium in Solution: Consequences For CO_2 Reduction Mechanisms. *Chem. Sci.* **2013,** *4*, 1490-1496.

31. Lucio, A. J.; Shaw, S. K., Pyridine and Pyridinium Electrochemistry on Polycrystalline Gold Electrodes and Implications for CO_2 Reduction. *J. Phys. Chem. C* **2015,** *119*, 12523-12530.

32. Mejía, E.; Luo, S.; Karnahl, M.; Friedrich, A.; Tschierlei, S.; Surkus, A.; Junge, H.; Gladiali, S.; Lochbrunner, S.; Beller, M., A Noble-Metal-Free System for Photocatalytic Hydrogen Production from Water. *Chem. - Eur. J.* **2013,** *19*, 15972-15978.

33. Pletcher, D.; Green, R. A.; Brown, R. C. D., Flow Electrolysis Cells for the Synthetic Organic Chemistry Laboratory. *Chem. Rev.* **2018,** *118*, 4573-4591.

34. Möhle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R., Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products. *Angew. Chem., Int. Ed.* **2018,** *57*, 6018-6041.

35. Rogers, F. J. M.; Coote, M. L., Computational Evaluation of the Oxidative Cleavage of Triazine Derivatives for Electrosynthesis. *J. Phys. Chem. C* **2019,** *123*, 10306-10310.

36. Rogers, F. J. M.; Coote, M. L., Computational Assessment of Verdazyl Derivatives for Electrochemical Generation of Carbon-Centered Radicals. *J. Phys. Chem. C* **2019** *123*, 20174-20180.

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