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Electrochemical oxidative CF_3 radical-induced lactonization and etherification of terminal and internal alkenes†

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Introducing trifluoromethyl (CF_3) groups enhances drug candidates' properties, improving metabolic stability and bioavailability. This study reports the electrochemical oxidation of Langlois' reagent for CF_3 radical-promoted cyclization, synthesizing functionalized lactones and cyclic ethers from terminal and internal alkenes with good to high yields. Mechanistic insights were supported by cyclic voltammetry, radical scavenger experiments, and DFT calculations. The protocol's efficiency highlights its potential in medicinal chemistry for developing pharmacologically valuable compounds avoiding the use of rare metal electrodes.

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Introduction

The introduction of fluorine atoms into organic molecules has gained significant interest due to their ability to considerably enhance the properties of bioactive compounds.[1] This is particularly evident in pharmaceutical[2] and agrochemical[3] sectors, where fluorinated compounds account for approximately 20% and 50% of the market, respectively. The trifluoromethylated derivatives are widely used in medicinal chemistry since the trifluoromethyl group (CF_3) is small and highly electronegative, and its incorporation into parent compounds can significantly alter their physical and chemical properties.[4] Trifluoromethylation methodologies have made notable progress along the years, particularly through the application of transition metal catalysis and photoredox systems employing electrophilic trifluoromethylation agents like Togni's and Umemoto's reagents,[5] or nucleophilic ones such as the Ruppert–Prakash reagent.[6] These radicals have been applied to the difunctionalization of alkenes, resulting in reactions like aminotrifluoromethylation,[7] oxytrifluoromethylation,[8] hydrotrifluoromethylation[9] and halotrifluoromethylation.[10] Although these methods are synthetically valuable, the reliance on stoichiometric amounts of chemical oxidants or reductants leads to the production of harmful wastes and significantly restricts the compatibility with various functional groups, limiting the scope. Recently, electro-organic synthesis has gained renewed attention for its environmentally friendly approach to redox transformations and cost-effective processes.[11] This technique offers a promising alternative to using excess redox reagents and helps to significantly minimize the generation of toxic by-products.

Among available reagents for CF_3 radical generation, Langlois' sulfinate ($NaSO_2CF_3$) is particularly appealing due to its stability, low cost, and commercial accessibility.[12] As a result, its usage emerged as a promising strategy for synthesizing CF_3-containing compounds.[13]

Lactones and cyclic ethers are important components in many pharmaceutical compounds, and the development of CF_3-containing derivatives could offer significant advantages in medicinal chemistry.[14] In 2012 and 2013, Buchwald introduced a versatile method for the rapid synthesis of various enantiomerically enriched lactones and cyclic ethers, using copper as a catalyst and Togni's reagent as CF_3 source (Fig. 1).[15] Few years later, Akita and coworkers developed the first example of trifluoromethylative lactonization of both terminal and internal alkenoic acids using ruthenium photoredox catalysis, with the Umemoto's reagent as CF_3 source.[16] Despite the rapid development of electro-organic chemistry, only one example of electrochemical lactonization of terminal alkenes has been reported so far by Xu and coworkers, in which a CF_2X group is installed using $NaSO_2CF_2H$ and $NaSO_2CF_3$.[17] This reaction using Pt electrode at the anode and cathode in the presence of water was limited in terms of chemical architecture to the formation of five members ring lactones from benzoic acid derivatives, with diphenylmethyl carbon moieties.

Regarding the synthesis of cyclic ethers mediated by trifluoromethylation, in addition to Buchwald's work, Liu's group has made significant contributions by utilizing copper catalysts for the cyclization of alkenes.[18] On the other hand, several

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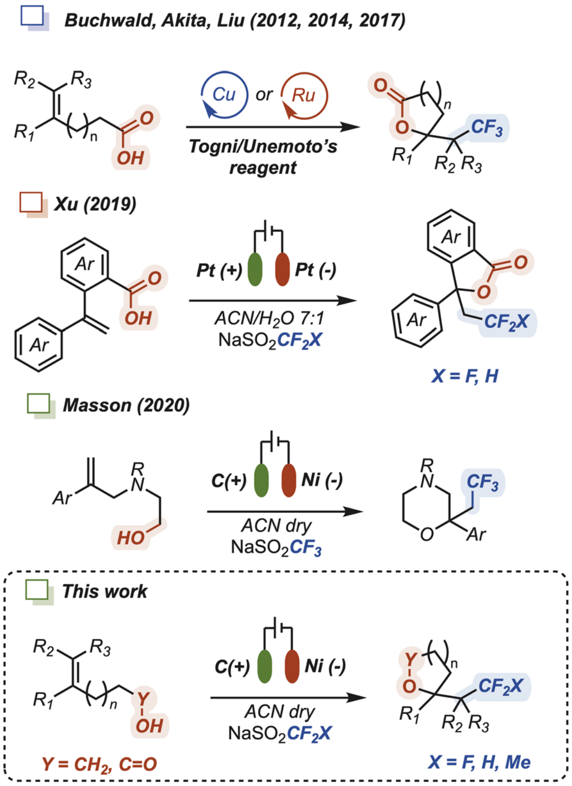


Fig. 1 State of the art of the CF_3 induced lactonization and etherification.

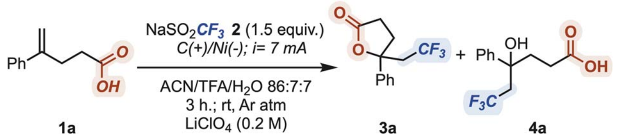
studies have explored the use of Langlois' reagent in electrochemical approaches to cyclic ether synthesis. Wu (with Mn(II) catalysts),[19a] and Gao/Zhu,[19b] performed the indole dearomatization taking advantage of the rigid indole scaffold and using as nucleophiles alcohols or NHTosylate, to generate indolines using both the Langlois' reagent. Clarez and Masson also reported the formation of cyclic morpholino derivatives based on a similar strategy.[20] Despite these advances, a general procedure for synthesizing various fluorinated cyclic ethers through electrochemical methods is still lacking.

Inspired by these works, our target was the development of a versatile general protocol for the electrochemically promoted oxidative difunctionalization of flexible terminal and internal alkenes to produce trifluoromethyl substituted lactones and ethers avoiding the use of metal catalysts or electrodes made of rare metals.[21] This approach eliminates the need for oxidants, reductants, catalysts, or transition metals, enabling direct electrolysis at room temperature to produce the desired CF_3 containing lactones and ethers.

Results and discussion

The reaction between 4-phenylpent-4-enoic acid **1a** and 1.5 equivalents of $NaSO_2CF_3$ **2a** in acetonitrile (ACN) performed in an undivided cell under argon at room temperature was used to screen different variables for the lactonization process (Table 1). The initial study was performed using graphite at the cathode and nickel at the anode in ACN/trifluoroacetic acid (TFA)/H_2O (86/7/7) solvent mixture, using $LiClO_4$ (0.2 M) as electrolyte, under a constant current of 7 mA for 3 hours. The target products **3a** was quantified by ^{19}F NMR against standard (Table 1, Entry 1). In addition to **3a** the corresponding open hydroxylated byproduct **4a** was generated with a 12% yield. To confirm the role of the electrochemical oxidation, the reaction performed without electrical current didn't afford any product (Entry 2). Based on these preliminary results, we screened various parameters in order to enhance the selectivity and yield of the reaction. Replacing TFA with acetic acid in an attempt to enhance discharge at the cathode resulted in a decrease in reaction performance (Entry 3), demonstrating the efficiency of TFA for this purpose. Accordingly, reducing the amount of TFA to 5% lowered the yield to 80% (Entry 4) and no significant improvements were observed increasing the TFA concentration to 10% (Entry 5). Increasing the current to 10 mA or decreasing it to 5 mA led to a further decline in product yield (Entries 6–7). Variation in electrode materials resulted in a significant drop in yield when Pt was used as anode in place of Ni or when RVC (Reticulated Vitreous Carbon) was employed as cathode (Entries 8–9). The use of Pt at both, anode and cathode showed a consistent yield drop (Entry 10), while the use of graphite allowed to get a 74% yield (Entry 11).

Table 1 Optimization of the electrochemical CF_3-induced lactonization



Entry[a]	Variations	3a[b]	4a
1	None	84	12
2	No current	0	0
3	AcOH instead of TFA	60	30
4	TFA 5%	80	15
5	TFA 10%	85	10
6	5 mA	66	17
7	10 mA	72	10
8	C(+)/Pt(−)	71	1
9	RVC(+)/Ni(−)[c]	40	17
10	Pt(+)Pt(−)	12	6
11	C(+)/C(−)	74	6
12	$LiBF_4$ as electrolyte	68	26
13	$TBAClO_4$ as electrolyte	81	10
14	3.0 equiv. of **2**	78	13
15	No **2**	0	0
16	No water	89 (80)[d]	0
17	C(+)/Pt(−); no water	67	0
18	Pt(+)/Pt(−); no water	41	0
19	C(+)/C(−) no water	64	0
20	C(+)/C(−) divided cell, no water	32	0

[a] All the reactions were performed with 0.15 mmol scale using IKA electrasyn 2.0. [b] Yield calculated using $PhCF_3$ as internal standard. [c] C = graphite; RVC = reticulated vitreous carbon. [d] Isolated yield.

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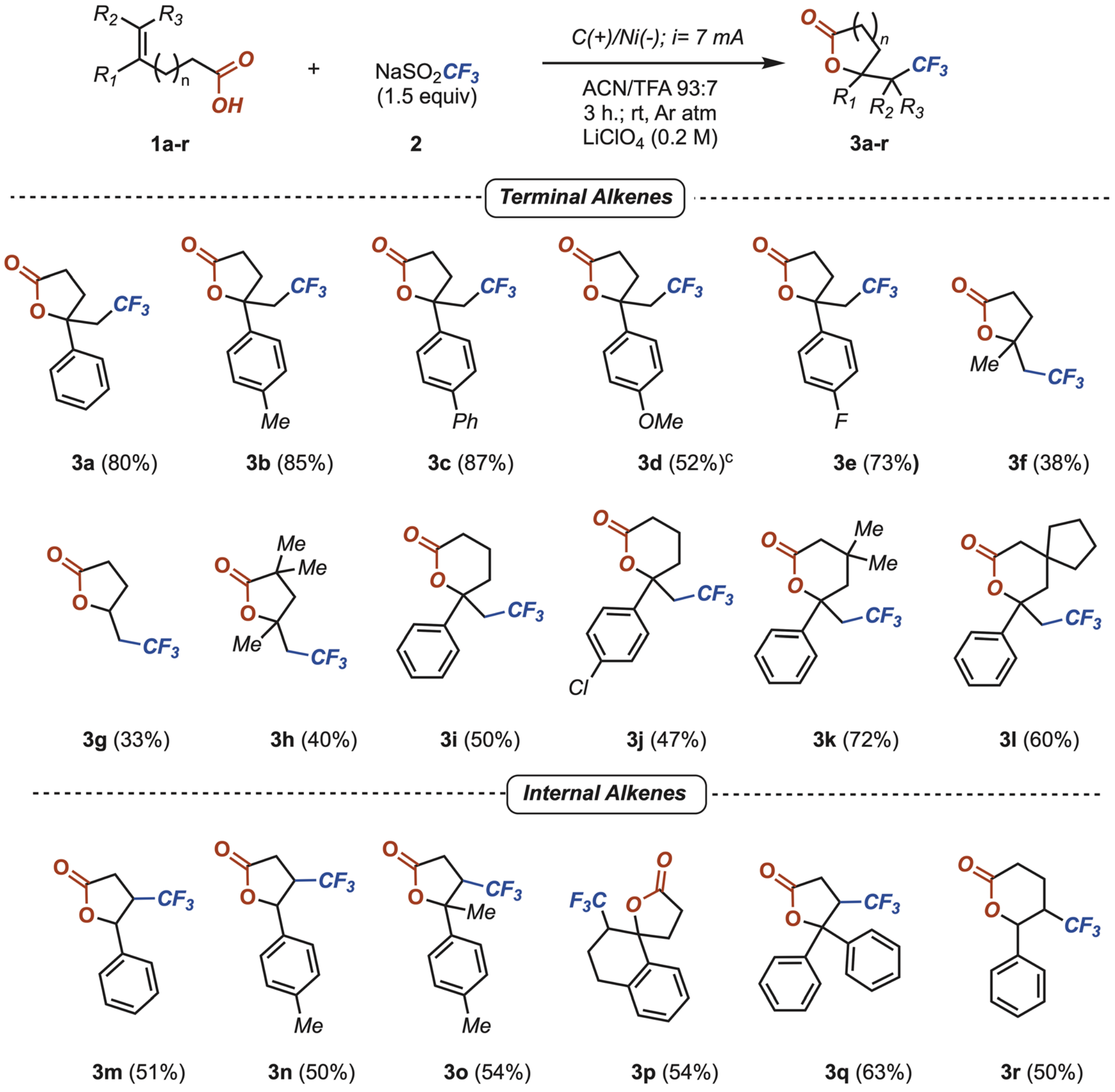
Changing the electrolyte to $LiBF_4$ or $TBAClO_4$ proved to be ineffective in improving the reaction efficiency (Entries 12–13). A decrease in yield was observed when the amount of CF_3SO_2Na was enhanced to 3.0 eq., due to the more favorable formation of the hexafluoroethane byproduct (Entry 14). Noticing that higher TFA levels improved the yield, we tested its role in trifluoromethylation *via* Kolbe electrolysis by omitting the Langlois' reagent. No **3a** was formed, confirming CF_3SO_2Na is the only responsible for the trifluoromethylation (Entry 15). While the byproduct **4a** was present in all the above-described reactions, it was completely suppressed in the absence of water, which acts as more competitive nucleophile than the carboxylic acid. Repeating the best reaction from Entry 1 under anhydrous conditions enabled us to achieve an 89% ^{19}F NMR yield and an 80% isolated yield (Entry 16). The combination of C(+)/Pt(−), Pt(+)/Pt(−) and C(+)/C(−) electrodes allowed to get a 67%, 41% and 64% yield, respectively (Entries 17–19). Other variants studied under anhydrous conditions, such as acid or electrolyte elimination, substitution of TFA with AcOH or hexafluoro isopropanol, did not improve the reaction outcome, see the complete optimization study in Table S1.† A similarly negative impact was observed when using a divided cell, entry 20.

The best result in Table 1 was obtained using the C(+)/Ni(−) combination under anhydrous conditions (Entry 16).

With the optimized conditions in hand, we explored the scope of the electrochemical lactonization triggered by CF_3SO_2Na. Notably, all the experiments described within the reaction scope were carried out using graphite (+) and Ni (−) as electrodes under anhydrous conditions and the side product **4** was never observed.

The optimized protocol using terminal alkenes **3a–l** as well as internal ones **3m–r** (Scheme 1) demonstrated the versatility of the protocol. The five-membered lactone ring was obtained in good yields when the formed carbocation was stabilized in the benzylic position, such as in **3a–3e**. On the other hand, replacing the aryl group with more challenging aliphatic carboxylic



Scheme 1 Substrate scope of the electrochemical di- and trifluoro lactonization.[a,b] [a] All the reactions were performed with 0.15 mmol scale using IKA electrasyn. [b] Isolated yields. [c] Reaction performed with 86/7/7 ratio of $ACN/H_2O/TFA$.

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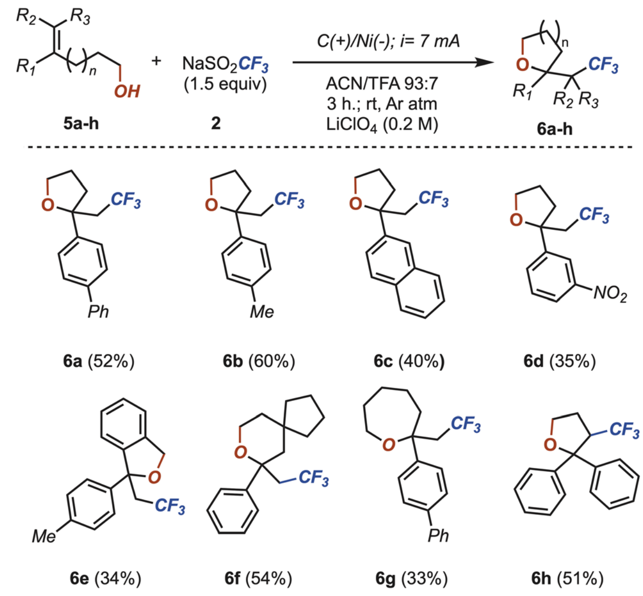

Scheme 2 Substrate scope of the electrochemical CF_3-induced etherification.[a,b] [a] All the reactions were performed with 0.15 mmol scale using IKA electrasyn. [b] Isolated yields.

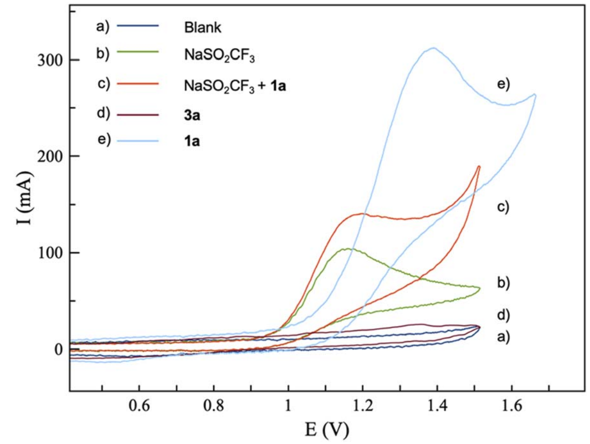

Fig. 2 Cyclic voltammograms of substrate **1a** in 0.1 M $LiClO_4$/ACN, using a Glassy Carbon (GC) as working electrode, Pt as counter electrode and Fc/Fc+ (0.1 M in ACN) as internal standard.

acids substrates led to the formation of the corresponding lactones **3f–3h** in yields ranging from 33% to 40%, likely due to the formation of a less stabilized radical/carbocation intermediate after CF_3 radical insertion. The methodology was also effective in forming six-membered lactones as demonstrated by **3i–3l**. The presence of alkyl substituents along the chain enhanced intramolecular cyclization, significantly increasing the yields (**3k** and **3l**). As the first reported example in the literature, the reaction was successfully extended to internal flexible alkenes, demonstrating the protocol's versatility in forming a single anti-diastereoisomer, as confirmed by NMR analysis (Fig. S4†), **3o–3r**. Independently from the substrate, we achieved almost the same yields 50–63%. To scale up the reaction to a 1 mmol scale, the concentration was increased from 25 mM to 55 mM, due to limitation in the volume of vessels compatible with Electrasyn apparatus. This adjustment resulted in a lower yield, from 80% to 63% (see Chapter 6 of SI).

The procedure used for the lactonization process was extended to the formation of cyclic ethers **6a–6h**, see Scheme 2. As in the lactonization process, maintaining anhydrous conditions suppressed the formation of the corresponding benzylic alcohols. The lower nucleophilicity of the alcohol compared to the carboxylic acid led to a decrease in final product yields, ranging from 33% to 60%.

The reaction proceeded efficiently with EDG groups (**6a–c**), while the presence of a nitro group in the *meta* position of the aromatic ring destabilized the radical/carbocation intermediate, further reducing the yield to 35%, as observed for compound **6d**. The reaction also enabled the formation of valuable substrates, such as benzofurans (**6e**) with a satisfactory yield, as well as six-membered cyclic ethers (**6f**). Additionally, the protocol facilitated the synthesis of seven-membered rings and proved to be effective for internal alkenes, as demonstrated by products **6g** and **6h**, respectively.

Reaction mechanism

The cyclic voltammetry (CV) experiments were performed to better understand the oxidation potentials of the species involved in the process (Fig. 2). The CV were conducted in the reaction conditions described in Fig. 2. The oxidative peak of CF_3SO_2Na **2** was observed at 1.17 V *vs.* [Fc/Fc^+] (Fig. 2, experiment b), while the alkene displayed an oxidative peak at 1.40 V *vs.* Fc/Fc^+ (Fig. 2, experiment e). This indicates that the Langlois' reagent is more readily oxidized than the alkene. Notably, when the alkene was introduced into the system (Fig. 2, experiment c), the oxidative peak remained consistent with that of CF_3SO_2Na, emphasizing that only the Langlois' reagent undergoes oxidation. Furthermore, the product **3a** was found to be completely stable, as no additional oxidation peaks were detected (Fig. 2, experiment d).

Furthermore, the addition of a radical scavenger such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT) completely suppressed the reaction (see Chapter 6 of ESI†). BHT was also able to trap the F_3C. Radical

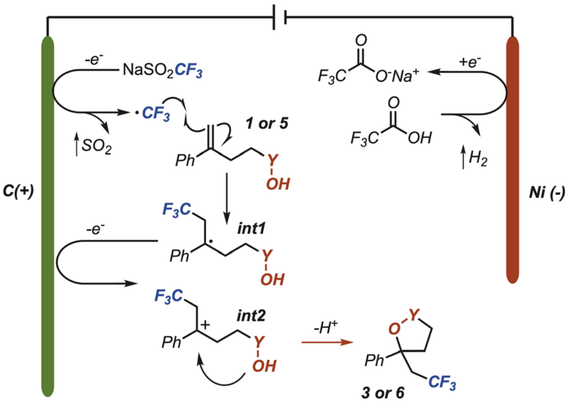

Fig. 3 Plausible mechanism of the oxidative trifluoromethylation of alkenes.

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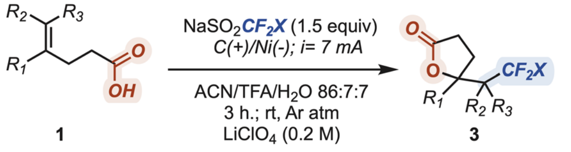

Substrate	Product
1b	**3b** 85% (X = F) **3s** 53% (X = H)
1e	**3e** 73% (X = F) **3t** 42% (X = Me)
1q	**3q** 63% (X = F) **3u** 35% (X = H)

Scheme 3 Reactivity comparison of different substituents on the Langlois' reagent.

generating the corresponding ether, for details see page S28.† All the data supported the mechanism *via* anodic single-electron transfer (SET) oxidation of CF_3SO_2Na that produces the CF_3 radical *via* the release of SO_2 from the CF_3SO_2 intermediate. This electrophilic CF_3 radical reacts with the alkene **1** or **5**, forming the radical intermediate **int1** (Fig. 3). A second anodic SET oxidation converts intermediate **int1** into cation **int2**. The reaction ends with an intramolecular nucleophilic attack by the nucleophilic moiety, achieving the trifluoromethyl substituted product **3** or **6** and releasing H^+ ions. The H^+ ions are then reduced at the cathode, a process further facilitated by the presence of TFA.

To better understand the reactivity of different substituents on the Langlois' reagent, additional control experiments were conducted. As shown in Scheme 3, replacing $NaSO_2CF_3$ with $NaSO_2CF_2H$ or $NaSO_2CF_2Me$ led to significantly lower yields (**3s**, **3t** and **3u**, Scheme 1). This reduction in yield can likely be attributed to a polarity mismatch, as CF_2H and CF_2Me radicals exhibit greater nucleophilicity compared to the CF_3 radical, making them less compatible with the reaction conditions.

In this context, Density Functional Theory (DFT) calculations were conducted to gain deeper insights into how substituents on the Langlois' reagent $NaSO_2CF_2X$ (X = F, H, Me) influence the reaction efficiency (Fig. 4). The reaction coordinate for the addition of the CF_2X radical to alkene **1h** was computed (Fig. 4a). As expected, the transition state (**TS1**) for the addition of the CF_3 radical exhibits a lower energy barrier (1.2 kcal mol^{-1}) compared to CF_2H and CF_2Me (2.8 and 3.6 kcal mol^{-1}, respectively). The electrophilic CF_3 radical reacts more favorably with the electron-rich double bonds (see Fig. S5†).

To further understand the impact of different substituents during the cyclization step leading to intermediate **D**, we separately calculated the transition states for this step (**TS2**) to minimize potential errors introduced by the oxidation of intermediate **B** to intermediate **C** (Fig. 4b). The results reveal that **TS2** for CF_2X species is very close, being X one carbon away from the carbocation **C**. As expected, the main impact of X is on the formation of **B**.

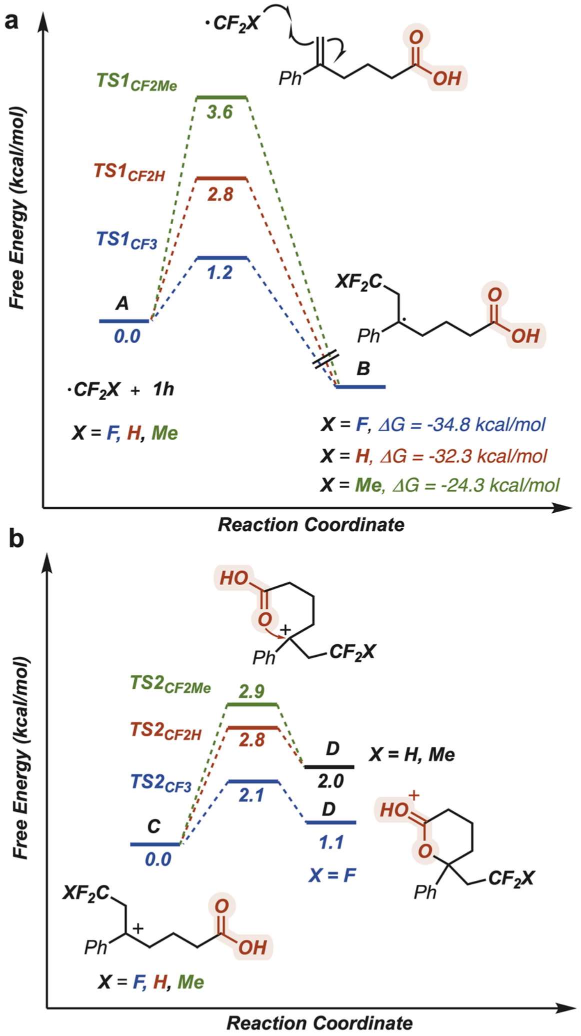

Fig. 4 DFT-calculation-computed reaction profile and solution-state Gibbs free energies (Δ*G*(ACN), kcal mol^{-1}) B3LYP/DEF2-TZVP level of theory at 298 K. (a) CF_2X attack on the double bond. (b) Cyclization.

These computational findings align with experimental observations in Scheme 3, demonstrating that reactions with CF_3 result in higher yields compared to CF_2H and CF_2Me, validating the importance of the electronic properties of substituents in driving the reaction efficiency.

Conclusions

Summing up, we have developed an efficient metal- and mediator-free electrochemical method for synthesizing lactones and cyclic ethers *via* sequential tri- and difluoromethylation followed by cascade cyclization. This versatile protocol represents the first example of electrochemical CF_3-induced lactonization of internal alkenes. Utilizing the bench-stable Langlois' reagent, the reaction operates under mild conditions at room temperature in an undivided cell with inexpensive graphite and nickel electrodes. Mechanistic studies, including cyclic voltammetry, radical scavenger experiments and DFT calculations, confirmed the single electron oxidation radical pathway.

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Data availability

The data supporting this article have been included as part of the ESI.† Raw data comprising NMR FID of this article compounds and the protocols are available at AMSActa Institutional Research Repository DOI: **https://doi.org/10.6092/unibo/amsacta/8336**.

Author contributions

RG, and TF contribute equally to the work. RG, TF, ML and GA performed the reactions and analysis. TF performed the DFT studies. AT and LF performed data reviewing. WC and TF were responsible for conceptualization. The manuscript was written through contributions of all authors. All authors have given approval for the final version of the manuscript.

Conflicts of interest

There are no conflicts of interest to declare.

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References

1 (*a*) W. K. Hagmann, The Many Roles for Fluorine in Medicinal Chemistry, *J. Med. Chem.*, 2008, **51**, 4359; (*b*) K. Müller, C. Faeh and F. Diederich, Fluorine in Pharmaceuticals: Looking Beyond Intuition, *Science*, 2007, **317**, 1881; (*c*) S. Purser, P. Moore, S. Swallow and V. Gouverneur, Fluorine in medicinal chemistry, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*d*) J. Wang, M. Sanchez-Rosello, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011), *Chem. Rev.*, 2014, **114**, 2432–2506.

2 M. Inoue, Y. Sumii and N. Shibata, Contribution of Organofluorine Compounds to Pharmaceuticals, *ACS Omega*, 2020, **5**, 10633–10640.

3 Q. Wang, H. Song and Q. Wang, Fluorine-containing agrochemicals in the last decade and approaches for fluorine incorporation, *Chin. Chem. Lett.*, 2022, **33**, 626–642.

4 (*a*) O. A. Tomashenko and V. V. Grushin, Aromatic Trifluoromethylation with Metal Complexes, *Chem. Rev.*, 2011, **111**, 4475; (*b*) A. A. Studer, "Renaissance" in Radical Trifluoromethylation, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950; (*c*) H. Egami and M. Sodeoka, Trifluoromethylation of Alkenes with Concomitant Introduction of Additional Functional Groups, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294; (*d*) E. Merino and C. Nevado, Addition of CF_3 across unsaturated moieties: a powerful functionalization tool, *Chem. Soc. Rev.*, 2014, **43**, 6598; (*e*) T. Liang, N. Neumann and T. Ritter, Introduction of fluorine and fluorine-containing functional groups, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214; (*f*) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, Asymmetric construction of stereogenic carbon centers featuring a trifluoromethyl group from prochiral trifluoromethylated substrates, *Chem. Rev.*, 2011, **111**, 455.

5 (*a*) T. Umemoto and S. Ishihara, Power-variable electrophilic trifluoromethylating agents. S-, Se, and Te-(trifluoromethyl) dibenzothio-, -seleno-, and -tellurophenium salt system, *J. Am. Chem. Soc.*, 1993, **115**, 2156–2164; (*b*) L. Mei, J. Moutet, S. M. Stull and T. M. Gianetti, Synthesis of CF_3-Containing Spirocyclic Indolines *via* a Red-Light-Mediated Trifluoromethylation/Dearomatization Cascade, *J. Org. Chem.*, 2021, **86**, 10640–10653; (*c*) G. Levitre, G. Dagousset, E. Anselmi, B. Tuccio, E. Magnier and G. Masson, Four-Component Photoredox-Mediated Azidoalkoxy-trifluoromethylation of Alkenes, *Org. Lett.*, 2019, **21**, 6005–6010; (*d*) J. Charpentier, N. Früh and A. Togni, Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents, *Chem. Rev.*, 2015, **115**, 650–682; (*e*) H. Zhu, C. Gao, T. Yu, C. Xu and M. Wang, O-Trifluoromethylation of Carboxylic Acids *via* the Formation and Activation of Acyloxy(phenyl) trifluoromethyl-λ3-Iodanes, *Angew. Chem., Int. Ed.*, 2024, **63**, 16.

6 (*a*) I. Ruppert, K. Schlich and W. Volbach, *Tetrahedron Lett.*, 1984, **25**, 2195–2198; (*b*) T. Furukawa, T. Nishimine, E. Tokunaga, K. Hasegawa, M. Shiro and N. Shibata, Organocatalyzed Regio- and Enantioselective Allylic Trifluoromethylation of Morita–Baylis–Hillman Adducts Using Ruppert–Prakash Reagent, *Org. Lett.*, 2011, **13**(15), 3972–3975; (*c*) B. M. Trost, H. Gholami and D. Zell, Palladium-Catalyzed Asymmetric Allylic Fluoroalkylation/Trifluoromethylation, *J. Am. Chem. Soc.*, 2019, **141**(29), 11446–11451.

7 (*a*) L. Zheng, L. Cai, X. Zhuo, L. Deng, Y. Wu, B. Yang, Y. Wang and W. Guo, Direct intermolecular three-component aminotrifluoromethylation of styrenes by visible-light-photoredox catalysis, *Org. Chem. Front.*, 2022, **9**, 6498–6504; (*b*) V. Motornov, B. Klepetářová and P. Beier, Cu(III) Trifluoromethyl Complexes with 1,3-Diketonate Ligands and Their Versatile Reactivity in C–H Trifluoromethylation, *Adv. Synth. Catal.*, 2023, **365**, 2858–286; (*c*) N. Chen and S.-L. Zhang, Selective Intermolecular Dual Amino-Trifluoromethylation of Alkenes by High-Valent Cu(III)–CF_3 Compounds, *Adv. Synth. Catal.*, 2022, **364**, 3941–3947.

8 (*a*) Q. Li, W. Fan, D. Peng, B. Meng, S. Wang, R. Huang, S. Liu and S. Li, Cobalt–Tertiary-Amine-Mediated Hydroxytrifluoromethylation of Alkenes with CF_3Br and Atmospheric Oxygen, *ACS Catal.*, 2020, **10**, 4012–4018; (*b*) C.-T. Chen, Y.-P. Chen, B.-Y. Tsai, Y.-Y. Liao, Y.-C. Su,

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T.-C. Chen, C.-H. Lu, R. Fujii, K. Kawashima and S. Mori, Vanadyl Species Catalyzed 1,2-Oxidative Trifluoromethylation of Unactivated Olefins, *ACS Catal.*, 2020, **10**, 3676.

9 (*a*) N. J. W. Straathof, S. E. Cramer, V. Hessel and T. Noël, Practical Photocatalytic Trifluoromethylation and Hydrotrifluoromethylation of Styrenes in Batch and Flow, *Angew. Chem., Int. Ed.*, 2016, **55**, 15549–15553; (*b*) K.-J. Bian, Y.-C. Lu, D. Nemoto, S.-C. Kao, X. Chen and J. G. West, Photocatalytic hydrofluoroalkylation of alkenes with carboxylic acids, *Nat. Chem.*, 2023, **15**, 1683–1692; (*c*) D. Peng, W. Fan, X. Zhao, W. Chen, Y. Wen, L. Zhang and S. Li, Zinc-Brønsted acid mediated practical hydrotrifluoromethylation of alkenes with CF_3Br, *Org. Chem. Front.*, 2021, **8**, 6356–6363; (*d*) Y.-F. Yang, J.-H. Lin and J.-C. Xiao, Starting from Styrene: A Unified Protocol for Hydrotrifluoromethylation of Diversified Alkenes, *Org. Lett.*, 2021, **23**, 9277–9282; (*e*) G. M. F. Batista, P. P. de Castro, H. F. Dos Santos, K. T. de Oliveira and G. W. Amarante, Electron-Donor-Acceptor Complex-Enabled Flow Methodology for the Hydrotrifluoromethylation of Unsaturated β-Keto Esters, *Org. Lett.*, 2020, **22**, 8598–8602.

10 (*a*) Y. Ouyang, C.-L. Tong, X.-H. Xu and F.-L. Qing, Copper and Zinc Copromoted Bromo(chloro)trifluoromethylation of Alkenes and Alkynes with Trifluoromethanesulfonic Anhydride, *Org. Lett.*, 2021, **23**, 346–350; (*b*) D. Li, T. Mao, J. Huang and Q. Zhu, Copper-Catalyzed Bromodifluoroacetylation of Alkenes with Ethyl Bromodifluoroacetate, *J. Org. Chem.*, 2018, **83**, 10445–10452; (*c*) R. T. Kareem, B. Azizi, M. Asnaashariisfahani, A. Ebadi and E. Vessally, Vicinal halo-trifluoromethylation of alkenes, *RSC Adv.*, 2021, **11**, 14941–14955.

11 (*a*) M. Yan, Y. Kawamata and P. S. Baran, Synthetic Organic Electrochemical Methods since 2000: On the Verge of a Renaissance, *Chem. Rev.*, 2017, **117**, 13230–13319; (*b*) N. Sauermann, T. H. Meyer, Y. Qiu and L. Ackermann, Electrocatalytic C-H Activation, *ACS Catal.*, 2018, **8**, 7086–7103; (*c*) J. B. Parry, N. Fu and S. Lin, Electrocatalytic Difunctionalization of Olefins as a General Approach to the Synthesis of Vicinal Diamines, *Synlett*, 2018, **29**, 257–265; (*d*) E. J. Horn, B. R. Rosen and P. S. Baran, Synthetic Organic Electrochemistry: An Enabling and Innately Sustainable Method, *ACS Cent. Sci.*, 2016, **2**, 302; (*e*) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, Electrifying Organic Synthesis, *Angew. Chem., Int. Ed.*, 2018, **57**, 5594; (*f*) S. G. Sauer and S. Lin, An Electrocatalytic Approach to the Radical Difunctionalization of Alkenes, *ACS Catal.*, 2018, **8**, 5175; (*g*) C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu and L. Ackermann, Organic Electrochemistry: Molecular Syntheses with Potential, *ACS Cent. Sci.*, 2021, **7**, 415–431; (*h*) Y. Li, S. Dana and L. Ackermann, Recent advances in organic electrochemical functionalizations for specialty chemicals, *Curr. Opin. Electrochem.*, 2023, **40**, 101312.

12 M. Tordeux, B. Langlois and C. Wakselman, Reactions of bromotrifluoromethane and related halides. Condensations with dithionite and hydroxymethanesulfinate salts, *J. Org. Chem.*, 1989, **54**, 2452–2453.

13 (*a*) K. Mahanty, S. K. Saha, A. Haldera and S. De Sarkar, Mediator-free electrochemical trifluoromethylation: a cascade approach for the synthesis of trifluoromethylated isoxazolines, *Chem. Commun.*, 2023, **59**, 4467–4470; (*b*) S.-J. Chen, W.-Q. Zhong and J.-M. Huang, Electrochemical Trifluoromethylation and Sulfonylation of N-Allylamides: Synthesis of Oxazoline Derivatives, *J. Org. Chem.*, 2023, **88**, 12630–12640; (*c*) Z. Zhang, L. Zhang, Y. Cao, F. Li, G. Bai, G. Liu, Y. Yang and F. Mo, Mn-Mediated Electrochemical Trifluoromethylation/C(sp2)-H Functionalization Cascade for the Synthesis of Azahetero-cycles, *Org. Lett.*, 2019, **21**, 762–766; (*d*) Y. Li, L. Wang, S. Zhou, G. He and Y. Zhou, Electrochemical oxidative cyclization of N-allylamides for the synthesis of CF_3-containing benzoxazines and oxazolines, *RSC Adv.*, 2024, **14**, 154–159; (*e*) K. La-Ongthong, T. Chantarojsiri, D. Soorukram, P. Leowanawat, V. Reutrakul and C. Kuhakarn, Electrochemical trifluoromethylation of 2-isocyanobiaryls using CF_3SO_2Na: synthesis of 6-(trifluoromethyl) phenanthridines, *Org. Biomol. Chem.*, 2023, **21**, 4225–4236; (*f*) L. Liu, W. Zhang, C. Xu, J. He, Z. Xu, Z. Yang, F. Ling and W. Zhong, Electrosynthesis of CF_3-Substituted Polycyclic Quinazolinones *via* Cascade Trifluoromethy-lation/Cyclization of Unactivated Alkene, *Adv. Synth. Catal.*, 2022, **364**, 1319–1325; (*g*) J. Lan, K. Lin, X. Zhang and T.-S. Zhu, Stereoselective migratory heteroaryltrifluoromethylation of allylic amines *via* electrosynthesis, *Green Chem.*, 2022, **24**, 6138–6144; (*h*) Z. Li, L. Jiao, Y. Sun, Z. He, Z. Wei and W.-W. Liao, CF_3SO_2Na as a Bifunctional Reagent: Electrochemical Trifluoromethylation of Alkenes Accompanied by SO_2 Insertion to Access Trifluoromethylated Cyclic N-Sulfonylimines, *Angew. Chem., Int. Ed.*, 2020, **59**, 7266–7270; (*i*) Y. Y. Jiang, G. Y. Dou, K. Xu and C. C. Zeng, Bromide-catalyzed electrochemical trifluoromethylation/cyclization of N-arylacrylamides with low catalyst loading, *Org. Chem. Front.*, 2018, **5**, 2573–2577; (*j*) Z. Ruan, Z. Huang, Z. Xu, G. Mo, X. Tian, X. Y. Yu and L. A. Catalyst-Free, Direct Electrochemical Tri- and Difluoroalkylation/Cyclization: Access to Functionalized Oxindoles and Quinolinones, *Org. Lett.*, 2019, **21**, 1237–1240; (*k*) L. Zhang, G. Zhang, P. Wang, Y. Li and A. Lei, Electrochemical Oxidation with Lewis-Acid Catalysis Leads to Trifluoromethylative Difunctionalization of Alkenes Using CF_3SO_2Na, *Org. Lett.*, 2018, **20**, 7396–7399.

14 (*a*) J. J. Beck and S.-C. Chou, The Structural Diversity of Phthalides from the Apiaceae, *J. Nat. Prod.*, 2007, **70**, 891–900; (*b*) Y. Kim, S. Sengupta and T. Sim, Natural and Synthetic Lactones Possessing Antitumor Activities, *Int. J. Mol. Sci.*, 2021, **22**, 1052; (*c*) L. Lu, D. S. Harmalkar, Y. Choi and K. Lee, An Overview of Saturated Cyclic Ethers: Biological Profiles and Synthetic Strategies, *Molecules*, 2019, **24**, 3778.

15 (*a*) R. Zhu and S. L. Buchwald, Copper-Catalyzed Oxytrifluoromethylation of Unactivated Alkenes, *J. Am. Chem. Soc.*, 2012, **134**, 12462–12465; (*b*) R. Zhu and

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S. L. Buchwald, Enantioselective Functionalizationof Radical Intermediates in Redox Catalysis: Copper-Catalyzed Asymmetric Oxytrifluoromethylation of Alkenes, *Angew. Chem., Int. Ed.*, 2013, **52**, 12655–12658.

16 Y. Yasu, Y. Arai, R. Tomita, T. Koike and M. Akita, Highly regio- and diastereoselective synthesis of CF_3-substituted lactones *via* photoredox-catalyzed carbolactonization of alkenoic acids, *Org. Lett.*, 2014, **16**, 780–783.

17 Z. Zhang, L. Li, J. Zhang, J. Zhang, M. Xue and K. Xu, Electrochemical fluoromethylation triggered lactonizations of alkenes under semi-aqueous conditions, *Chem. Sci.*, 2019, **10**, 3181–3185.

18 Y.-F. Cheng, X.-Y. Dong, Q.-S. Gu, Z.-L. Yu and X.-Y. Liu, Achiral Pyridine Ligand-Enabled Enantioselective Radical Oxy-trifluoromethylation of Alkenes with Alcohols, *Angew. Chem., Int. Ed.*, 2017, **56**, 8883–8886.

19 (*a*) K. Mo, X. Zhou, J. Wu and Y. Zhao, Electrochemical Dearomatization of Indoles: Access to Diversified Fluorine-Containing Spirocyclic Indolines, *Org. Lett.*, 2022, **24**, 2788–2792; (*b*) J. Lan, S. Li, K. Lin, P. Zhou, W. Chen, L. Gao and T. Zhu, The eco-friendly electrosynthesis of trifluoromethylated spirocyclic indolines and their anticancer activity, *Org. Biomol. Chem.*, 2022, **20**, 3475–3479.

20 A. Claraz, T. Courant and G. Masson, Electrochemical Intramolecular Oxytrifluoromethylation of N-Tethered Alkenyl Alcohols: Synthesis of Functionalized Morpholines, *Org. Lett.*, 2020, **22**, 1580–1584.

21 B. J. Glaister and G. M. Mudd, The environmental costs of platinum–PGM mining and sustainability: Is the glass half-full or half-empty?, *Miner. Eng.*, 2010, **23**, 438–450.

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