A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* **2024**, e202413723

Link to VoR: https://doi.org/10.1002/anie.202413723

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10.1002/anie.202413723

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Strain-Release-Driven Electrochemical Skeletal Rearrangement of Non-Biased Alkyl Cyclopropanes/butanes

Jing Qi,[a] Chu Wang,[b] Gan Wang,[a] Patrick O'Neill,[c] Srinivas Reddy Dubbaka,*[d] Hwee Ting Ang,*[a] Xuebo Chen,*[b] Jie Wu*[a,e]

[a] Dr. J. Qi, G. Wang, Dr. H. T. Ang, Prof. Dr. J. Wu
Department of Chemistry, National University of Singapore, 4 Science Drive 2, Singapore 117544, Republic of Singapore
E-mail: hweeting@nus.edu.sg (H.T.A.), chmjie@nus.edu.sg (J.W.)

[b] Dr. C. Wang, Prof. Dr. X.B-Chen
Theoretical and Computational Photochemistry of the Chinese Ministry of Education, Chemistry College, Beijing Normal University, Beijing 100875, P. R. China
E-mail: xuebochen@bnu.edu.cn

[c] Prof. Dr. P. O'Neill
Pfizer Ireland Pharmaceuticals, Process Development Centre, Ringaskiddy, Co-Cork, Ireland, 637578

[d] Dr. S.-R. Dubbaka
Pfizer Asia Manufacturing Pte Ltd, Manufacturing Technology Development Centre (MTDC), Synapse Building, #05-17, 3 Biopolis Drive, Singapore, 138623, Republic of Singapore
E-mail: srinivasreddy.dubbaka@pfizer.com

[e] Prof. Dr. J. Wu
National University of Singapore (Suzhou) Research Institute, Suzhou 215123, P. R. China

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Abstract: Capitalizing the inherent strain energy within molecules, strain-release-driven reactions have been widely employed in organic synthesis. Small cycloalkanes like cyclopropanes and cyclobutanes, with their moderate ring strain, typically require dense functionalization to induce bias or distal activation of (hetero)aromatic rings via single-electron oxidation for relieving the tension. In this study, we present a pioneering direct activation of alkyl cyclopropanes/butanes through electrochemical oxidation. This approach not only showcases the potential for ring-opening of cyclopropane/butane under electrochemical conditions but also streamlines the synthesis of diverse oxazolines and oxazines. The applicability of our method is exemplified by its broad substrate scopes. Notably, the products derived from cyclobutanes undergo a formal ring contraction to cyclopropanes, introducing an intriguing aspect to our discoveries. These discoveries mark a significant advancement in strain-release-driven skeletal rearrangement reactions of moderately strained rings, offering sustainable and efficient synthetic pathways for future endeavours.

Introduction

The concept of ring strain, introduced by from Adolf von Baeyer in 1885, has been pivotal in understanding the stability of compounds.[1] Beyond bond angle distortion, factors like bond length distortion, torsional strain, nonbonded interactions, and rehybridization energy also contribute to 'strain'.[1b, 2] Regardless of its origin, these strain energies enhance the reactivity of small rings, leading to applications across various fields including total synthesis, molecule diversification, materials science, and bioorthogonal chemistry. In chemical synthesis, strain-release-driven reactions are a potent extension of the synthetic toolbox, with the driving force increasing as the difference in strain energy between substrate and product increases. Highly strained bicyclic strain rings (Scheme 1a), such as [1.1.1]propellanes (TCPs),[2] bicyclo[1.1.0]butanes (BCBs), azabicyclo[1.1.0]butanes (ABBs), and housanes, have been extensively explored for the synthesis of mono- and disubstituted bicyclo[1.1.1]pentanes,[3] cyclobutanes,[4] azetidines,[5] and cyclopentanes.[6] Strain energy has also been effectively leveraged in skeletal editing for ring contraction (e.g., Favorskii reaction and Arndt–Eistert reaction)[7] and expansion (e.g., Büchner ring expansion and transformation of pyrrole to pyridine).[8] Additionally, it has also been utilized in skeletal rearrangement (Scheme 1b) including the transformation of cyclopropenes with pendant enyne to arenes via a strained cyclopropane intermediate[9] and β-acetoxy substituted enone to the tricyclic core of fusoxysporone via a cyclobutane intermediate.[10] These transformations, driven by strain-release, offer efficient access to complex molecular scaffolds under very mild conditions.

Despite the extensive exploration of strain-release-driven reactions with bicyclic small rings, strategies for monocyclic strained rings like cyclopropanes and cyclobutanes remain underdeveloped due to their significantly lower strain energy. While heavily functionalized donor–acceptor cyclopropanes, owing to steric and/or electronic biases, readily undergo ring-opening reactions with good regioselectivities,[11] simple cyclopropanes, more commonly found in nature, are less reactive due to insufficient biases. Various strategies, including transition-metal catalysis[12] and Lewis acid electrophilic activation,[13] have been explored for their ring-opening reactions, but with limitations such as narrow substrate scopes, low reaction selectivity, and harsh reaction conditions, hindering their broader applicability in synthetic chemistry.

In recent decades, electro- and photochemistry, harnessing electrons and holes or light as "traceless" reagents within a broad redox window, have emerged as mild and sustainable

10.1002/anie.202413723

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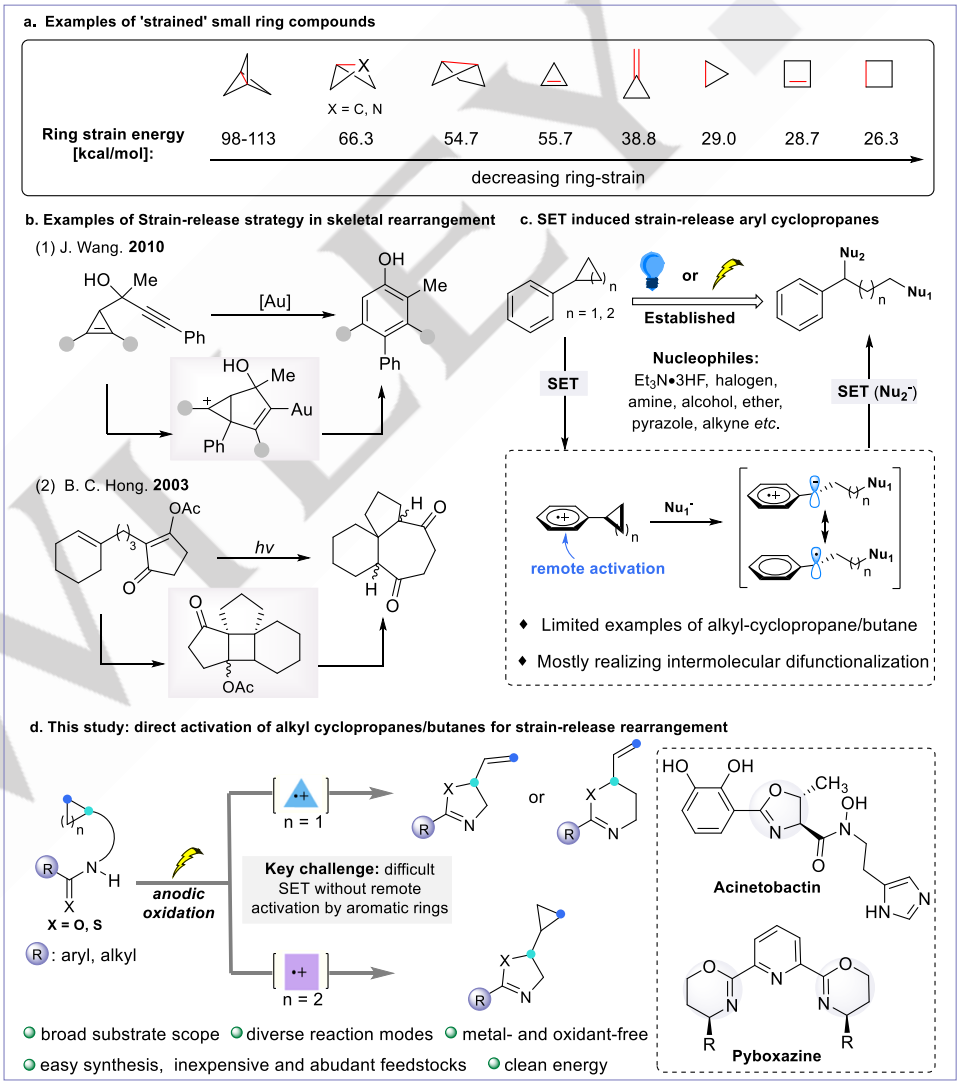
approaches for enabling numerous previously unachievable transformations.[14] Consequently, there has been a growing focus on exploring single-electron oxidation strategy by photochemical or electrochemical processes as a promising avenue for the activation of cyclopropanes/butanes for strain-release ring-opening functionalizations (Scheme 1c). For instance, Studer and co-workers achieved a radical cation-mediated ring-opening 1,3-difunctionalization of arylcyclopropanes with acyl fluorides by merging NHC and organophotoredox catalysis in 2021.[15] In the same year, Werz and co-workers demonstrated a catalyst-free strategy for C–C bond cleavage of aryl-cyclopropane and -cyclobutane through anodic oxidation to radical cations, which serve as electrophiles for the Friedel–Crafts type arylation reaction.[16] However, these methods are primarily applicable to arylcyclopropanes/butanes, relying on remote activation of the small rings through σ to SOMO orbital interaction of the aryl cation radical intermediates generated from single-electron oxidation of the aryl group.[17] Additionally, the reaction mode predominantly focuses on 1,3-difunctionalization reactions in an intermolecular fashion. Hence, there is a need for strategies that can broaden the scope of strain-release-drive reactions beyond arylcyclopropanes/butanes and diversify the types of reaction patterns, underscoring the ongoing efforts in research and the development of new protocols to address these challenges in strain-release-driven reactions of unactivated small rings.

In this work, we reported an electrochemical strain-release-driven rearrangement of alkylcyclopropanes/butanes with pendant (thio)amide moiety (Scheme 1d). Based on mechanistic studies, the reaction involves a direct activation of the small ring via single-electron oxidation, with the pendant amide group assuming a crucial role in facilitating the strain-release process via intramolecular cyclization following the oxidation. As a result, this approach yields a diverse array of oxazoline and oxazine compounds, serving as essential building blocks in natural products, biologically active compounds, and ligands for organic and asymmetric syntheses (e.g., BOX ligand,[18] pyboxazine[18b]), as well as fundamental scaffolds in pharmaceuticals such as acinetobactin,[19] etoxazole,[20] and poly(2-oxazoline),[21] recognized for their promising antitumor and antibacterial activities. Notably, the resulting product features a versatile alkene moiety, enabling further functionalization (Figure S13). Of particular interest is the observation that products derived from cyclobutanes undergo a formal ring contraction to cyclopropanes, adding an intriguing aspect to our findings.



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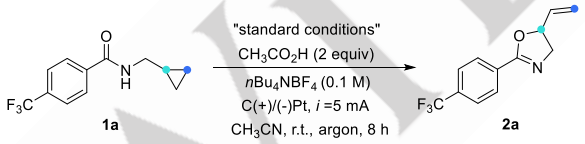
Scheme 1. Overview of Strain-Release-Driven Reactions and Our Work. (a) Examples of 'strained' small ring compounds. (b) Examples of Strain-release strategy in skeletal rearrangement. (c) SET induced strain-release aryl cyclopropanes. (d) This study: direct activation of alkyl cyclopropanes/butanes for strain-release rearrangement.

Results and Discussion

Screening of reaction conditions. Our investigation initiated with using *N*-(cyclopropylmethyl)-4-(trifluoromethyl)-benzamide (**1a**) as the model substrate to explore the reaction conditions (Table 1). Following systematic optimization, the vinyl oxazoline product **2a** was obtained in a 61% yield in CH_3CN under the conditions of a constant current of 5 mA in an undivided cell equipped with a graphite plate anode and a platinum plate cathode, with acetic acid as an additive at room temperature (entry 1). While the yield achieved was moderate, it is worth noting the clean reaction profile, with 29% of **1a** recovered after the reaction. The necessity of electricity was confirmed, as no reaction occurred in its absence (entry 2). Changing either the anode material (graphite to platinum or graphite felt) or the cathode material (platinum to nickel, iron, or stainless steel) resulted in decreased yields (entries 3-7). Additionally, under a constant voltage (4.0 V), a lower product yield was observed (entry 8). The presence of acid was found to significantly influence reaction efficiency, with the absence of acid yielding **2a** in 31% yield (entry 9), which could be attributed to its role in accelerating hydrogen evolution at the cathode and facilitating the reaction. Subsequent screening of various acids, including trifluoroacetic acid (TFA), trifluoromethanesulfonic acid, and pivalic acid, did not lead to improvements (entries 10-12). Finally, extending the reaction time to 24 hours did not enhance the yield; however, it resulted in a significant decrease in the recovery of unreacted **1a** (entry 13). This observation suggests that the reaction reached its maximum efficiency within the initially optimized timeframe, and further prolonging the reaction time led to either the decomposition of the starting material or the product.

Table 1. Optimization of reaction conditions [a]



Entry	variation from "standard conditions"	yield (%)[b]
1	none	61 (26)[c]
2	without electricity	0
3	Pt(+)/(-)Pt instead of C(+)/(-)Pt	trace
4	graphite felt (+)/(-)Pt instead of C(+)/(-)Pt	5
5	C(+)/(-)Ni instead of C(+)/(-)Pt	30
6	C(+)/(-)Fe instead of C(+)/(-)Pt	8
7	C(+)/(-)stainless steel instead of C(+)/(-)Pt	10
8	*V* = 4.0 V	15
9	no acid	30
10	TFA	5
11	CF_3SO_3H	20
12	$(CH_3)_3CCO_2H$	25
13	24 h	57 (9)[c]

[a] Standard conditions:**1a** (0.2 mmol, 1 equiv), nBu_4NBF_4 (0.5 mmol), CH_3CN (5 mL), C (graphite) anode, Pt (platinum) cathode (current intensity = 3.3 mA/cm^2), r.t. and i = 5 mA, undivided cell. [b] Isolated yield. [c] Recovered **1a**.

Substrate scope. With the optimal reaction conditions established, we explored the generality of this electro-oxidative strain-release ring-opening cyclization protocol using a variety of *N*-cyclopropylmethyl-aryl- and -alkyl-amides (Scheme 2). The reaction exhibited broad substrate compatibility with arylamides, accommodating a wide range of electron-neutral and electron-deficient substituents on the aromatic rings. Mono-substituted alkyl arenes, including methyl-, *tert*-butyl, and long-chain alkyl groups, underwent smooth reactions to provide the desired imide products (**2b**-**2g**) in moderate yields. Similarly, halide substituents (F, Cl, Br, and I) were also well tolerated, enabling the synthesis of the corresponding oxazolines (**2h**-**2k**) with synthetically useful yields. Moreover, electron-withdrawing groups such as nitrile, nitro, pinacol boronic ester, and esters showed good compatibility, yielding the desired products (**2l**-**2o**) effectively. Disubstituted aryl groups (**2p**-**2w**), including sterically hindered ones (**2x**), and fully deuterated phenylamides (**2y**) exhibited satisfactory reactivity. Moreover, heteroarenes such as pyridine and thiophene, which typically pose challenges under electrochemical conditions due to their susceptibility to oxidation, also engaged in the reaction, yielding the corresponding products (**2z**-**2ab**) with moderate yields. However, arenes with electron-donating groups (OMe, SMe, and OPh *etc.*) were not suitable in this protocol, due to the susceptibility of the electron-rich aryl ring to oxidation and subsequent decomposition on the electrode surface compared to the cyclopropane (Figure S14). In addition to *N*-cyclopropylmethyl arylamides, alkylamides proved to be viable substrates in this protocol, with tertiary alkyl groups (**2ad**) undergoing successful transformations in moderate yield (42%). Various cyclic structures, including cycloheptane, bicyclo[1.1.1]pentane, and adamantane rings, were compatible, yielding the desired products (**2ae**-**2ag**). Notably, even a derivative of (–)-camphanic acid produced the corresponding product (**2ah**) with a yield of 57%, demonstrating the potential of our protocol in late-stage modifications of complex bioactive molecules. Next, the scope of different substituents on the *N*-cyclopropylmethyl chain at *α*- or *β*-position of nitrogen was investigated. When the *α*-position is substituted with methyl (**2ai**), ester (**2aj**), cyclopropyl (**2ak**), and trifluoromethyl (**2al**), trisubstituted oxazolines were obtained in moderate yields, exclusively as *trans*-diastereomers due to steric control. Moreover, tetrasubstituted oxazoline (**2am** and **2an**) were obtained when the *α*-position is fully substituted, however, a 1:1 dr was observed for **2an** due to the lack of significant steric differences between the substituents (Me *vs* CO_2Me). Additionally, various functional groups at the *β*-position of nitrogen were compatible, resulting in the generation of quaternary carbon centers at the 5-position of oxazolines, regardless of their electronic neutrality (**2ar** and **2au**) or electron-withdrawing nature (**2as** and **2at**). Lastly, thioamides were also viable substrates in this protocol, yielding the corresponding thiazoline products in comparable yields to the

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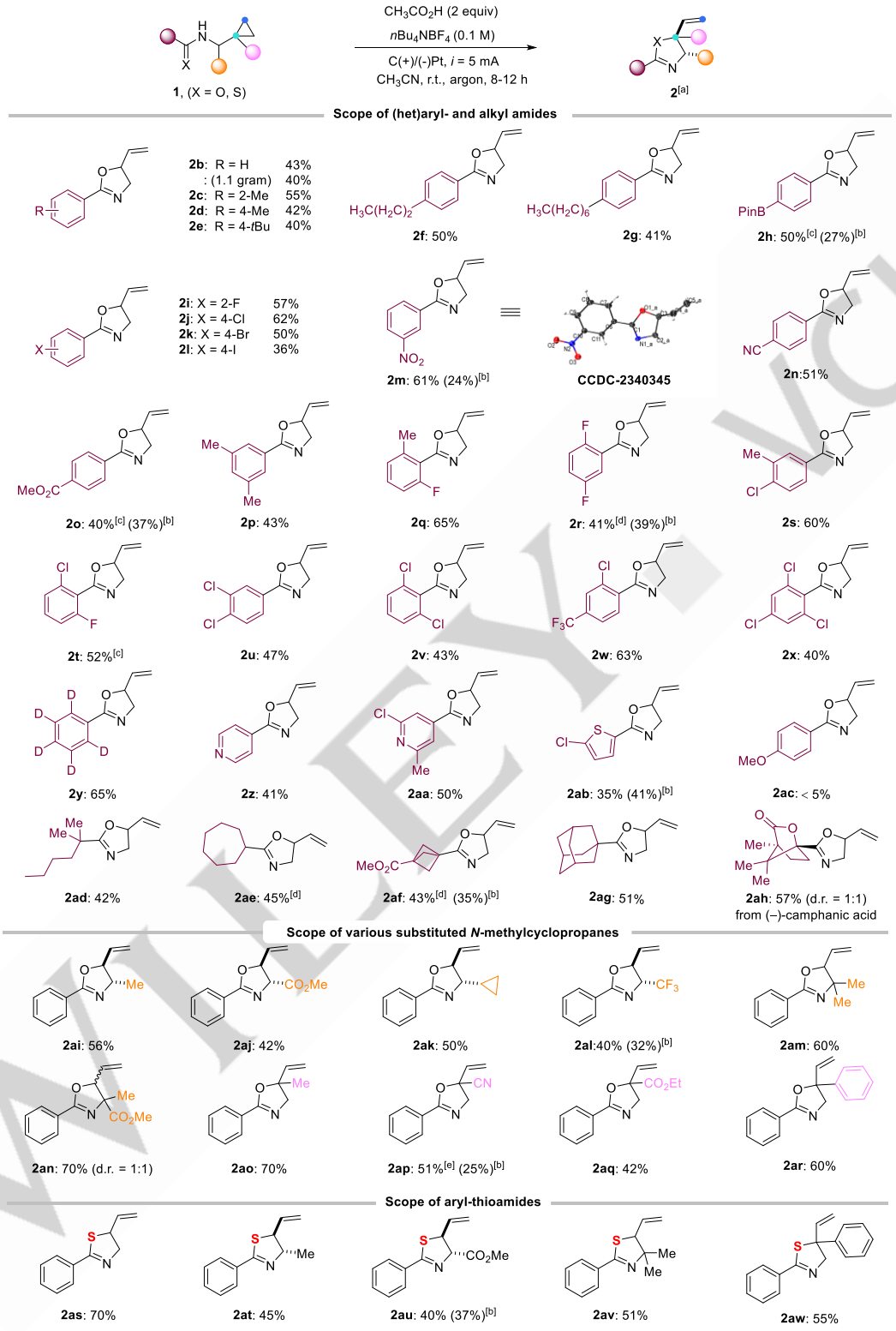
amides (**2as**-**2aw**). In general, while the yields achieved were moderate but synthetically useful, all reactions proceeded cleanly, facilitating the recovery and reuse of unreacted starting materials (e.g., **2h**, **2m**,[22] **2r**, **2ab**, **2af**, **2al**, **2ap**, and **2au**).



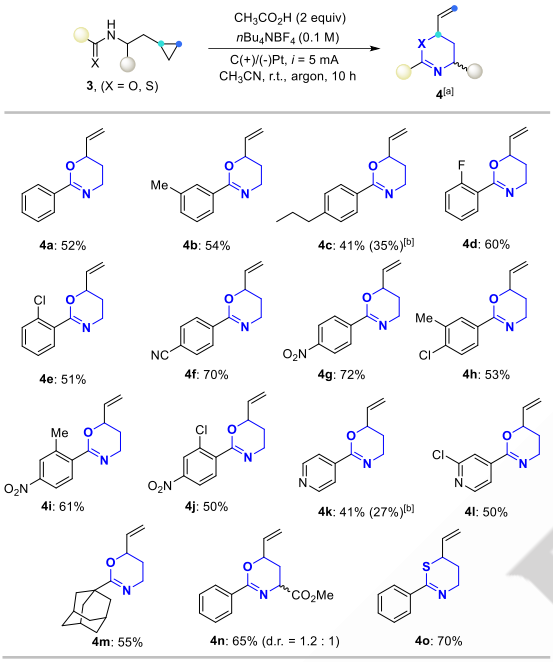
Scheme 2. Substrates scope of *N*-cyclopropylmethyl-amides. [a] Standard conditions: amide (0.2 mmol, 1 equiv), nBu_4NBF_4 (0.5 mmol), CH_3CN (5 mL), C (graphite) anode, Pt (platinum) cathode (current intensity = 3.3 mA/cm^2), r.t. and i = 5 mA, undivided cell; Isolated yields. [b] Yield of recovered starting materials. [c] Pt (platinum) anode, C (graphite) cathode. [d] Reaction time extended to 20 h. [e] Reaction time extended to 30 h.

The reaction could also be extended to *N*-(2-cyclopropylethyl) amides **3**, leading to the formation of a variety of oxazines

10.1002/anie.202413723

RESEARCH ARTICLE

(Scheme 3). Similar to the *N*-cyclopropylmethyl amides, aryl amides bearing various functional groups were compatible regardless of their electronic nature and substitution pattern, leading to moderate yields (**4a–4j**). Both pyridine (**4k**) and chloropyridine (**4l**) motifs were accommodated successfully. Furthermore, the transformation was applicable to alkylamides, such as adamantyl amide (**4m**), while maintaining good efficiency. Additionally, when the α-position of nitrogen was substituted with an ester, the trisubstituted oxazine (**4n**) was obtained in good yield, albeit with a 1.2:1 diastereoselectivity, owing to limited steric control resulting from spatial separation between the two substituents.



Scheme 3. Substrates scope of *N*-(2-cyclopropylethyl) amides [a] Standard conditions: amide 3 (0.2 mmol, 1 equiv), nBu_4NBF_4 (0.5 mmol), CH_3CN (5 mL), C (graphite) anode, Pt (platinum) cathode (current intensity = 3.3 mA/cm^2), r.t. and i = 5 mA, undivided cell; Isolated yields. [b] Yield of recovered starting materials.

Mechanistic investigations. Having successfully obtained cyclic compounds using *N*-cyclopropylmethyl/ethyl amides as substrates, we aimed to extend this approach to amides with longer carbon chains for the synthesis of larger cyclic compounds. However, upon preparation of *N*-cyclopropyl-propyl and -butyl amides (n = 3 and 4, respectively) and subjecting them to standard reaction conditions, no reaction occurred, and the starting materials were recovered (Scheme 4a).

In response, we conducted several mechanistic studies to gain insights into these transformations. Given that the substrates feature two potential oxidizable sites, the cyclopropane ring and the amidyl group, we employed density functional theory (DFT) to optimize the amidyl and cyclopropyl radical cations independently for all compounds with chain lengths (n) ranging from 1 to 4. These optimizations were performed at the M062X-D3/6-311G(d)/PCM level, and Gibbs free energies were calculated (Scheme 4b). The results reveal that the cyclopropyl radical cation is thermodynamically more stable than the corresponding amidyl radical cation across all compounds, suggesting a preference for the generation of the cyclopropyl radical cation during the anodic oxidation process. Further analysis into the free energy barriers of the cyclization steps (Scheme 4a and Figure S6) revealed minimal barriers for the methyl and ethyl chains (n =1 and 2), at 1.9 and 0.5 kcal·mol^{-1}, respectively, indicating smooth formation of five- and six-membered ring intermediates. However, larger barriers were observed for the propyl and butyl chains (n =3 and 4), at 5.0 and 6.6 kcal·mol^{-1}, respectively, suggesting challenges in the formation of seven- and eight-membered ring intermediates. Furthermore, transition state theory (TST) further estimated the cyclization rates to be at the nanosecond or below level for five- and six-membered rings (n = 1 and 2), but reached the sub-picosecond to picosecond level for seven- and eight-membered rings (n = 3 and 4). Thus, the ring formation for propyl and butyl chains was disfavored under both kinetic and thermodynamic considerations. Additionally, cyclic voltammetry (CV) experiments were conducted to evaluate the oxidation potentials of the four substrates (Figure S1), revealing additional oxidation peaks ($E_{p/2}$ = 2.16 V and $E_{p/2}$ = 1.99 V, *vs* Ag/AgCl in acetonitrile) corresponding to the cyclopropane rings of the shorter chain amides (n = 1 and 2, respectively), which were absent in the CV spectra of longer chain starting amides (n = 3 and 4). This finding also highlights the pivotal role of the pendant amide group not only in facilitating the cyclization step but also potentially in influencing the oxidation potential of cyclopropane rings.

In our investigation of different substitutions on cyclopropanes, we observed distinct regioselectivity in the reactions (Scheme 4c). Specifically, when a methyl group is introduced at the β-position of cyclopropane, it induces the cleavage of C_α–C_β bond, resulting in the formation of three distinct products. These products stem from deprotonation at different positions to yield alkenes (**5a** and **5a′**), along with nucleophilic substitution by a fluorine atom (from the electrolyte)[23] at a stabilized carbocation intermediate due the presence of the methyl group (**5a″**). Likewise, when the *β*-position is dialkylated (with dimethyl-, diethyl-, cyclobutyl groups), it leads to the cleavage of the C_α–C_β bond, yielding exclusively products with fluorine substitution (**6a**, **6b**, and **6c**). This outcome arises from the further stabilization of the carbocation intermediate by the dialkyl substituents, promoting fluoride substitution. Lastly, when *β*, *β*, *γ*, *γ*-tetramethyl-substituted cyclopropane was employed, oxazines **7a** and **7a′** were obtained through the cleavage of C_β–C_γ bond. These findings align with a recent study by Jirgensons and co-workers on the electrochemical formation of oxazolines by 1,3-oxyfluorination of non-activated cyclopropanes, utilizing the same substrate.[24] Contrary to their preliminary suggestion, based on prior literature, that the amidyl group undergoes oxidation to form an amidyl radical cation initiating the reaction, our computational analyses indicate that the oxidation of the cyclopropane forms a cyclopropyl radical cation triggering the reaction through strain-release.

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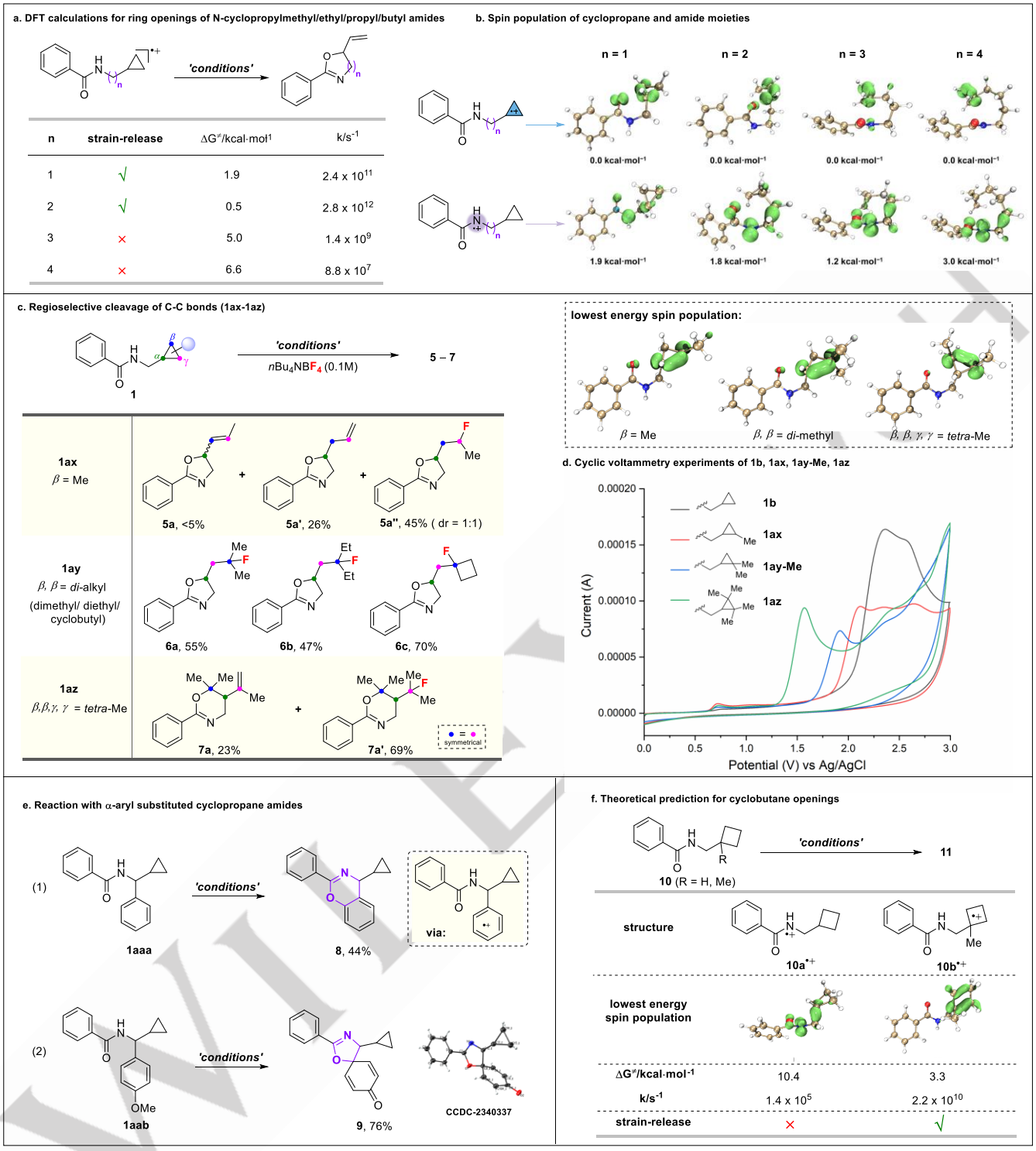

Scheme 4. Experimental and computational mechanistic investigations. (a) DFT calculations for ring openings of *N*-cyclopropylmethyl/ethyl/propyl/butyl amides. (b) Spin population of cyclopropane and amide moieties. (c) Regioselective cleavage of C–C bonds (**1ax-1az**). (d) Cyclic voltammetry experiments of **1b**, **1ax**, **1ay-Me**, **1az**. (e) Reaction with α-aryl substituted cyclopropane amides. (f) Theoretical prediction for cyclobutane openings.

To further elucidate the reactivity and selectivity differences induced by substituent groups on the cyclopropane ring, DFT (M062X-D3/6-311G(d) /PCM) calculations were conducted for substrates **1ax**, **1ay** (*β*, *β* = dimethyl), and **1az** (Figures S8-10). Spin population analysis of the lowest energy cyclopropyl radical cations revealed predominant electron localization at specific bond sites: at the C_α–C_β bond for *β*-Me and *β*, *β*-dimethyl substitutions; and at the C_β–C_γ bond for *β*, *β*, *γ*, *γ*-tetramethyl-substitution (Scheme 4c). The identified oxidized sites correspond to positions where more stable carbon radicals or carbocations would form following bond cleavage. These computational insights align with the bond-cleavage sites observed in the major

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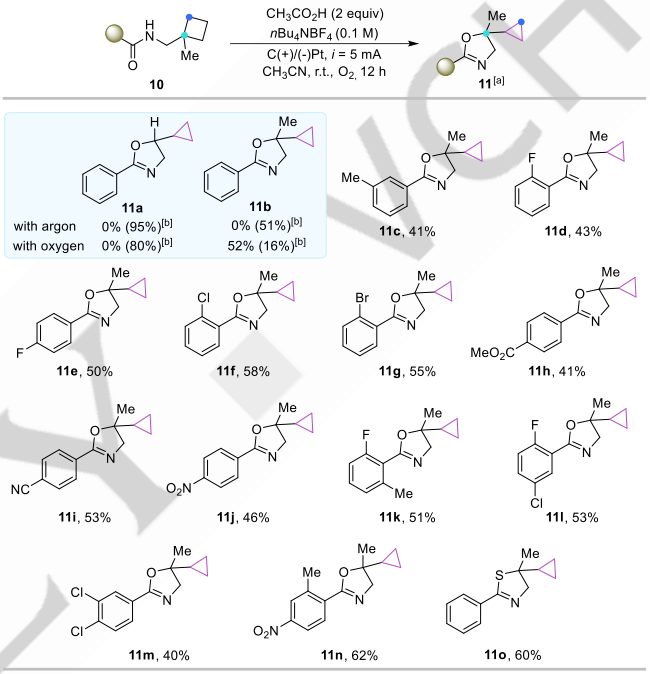
products obtained experimentally, thus explaining the observed selectivity with different substituents on the cyclopropane ring. Consequently, these results imply that the calculation of oxidized sites for such cyclopropane substrates can aid in predicting the bond-cleavage sites and generated major products. Additionally, the cyclic voltammetry (CV) experiments (Scheme 4d) for these four substrates exhibited a pronounced cathodic shift in oxidation peaks with an increased number of alkyl substituents. This observation provides further evidence of preferential oxidation at the cyclopropane ring, as the oxidation peaks would not significantly shift if the amide being oxidized instead.

Another set of substrates yielding differing outcomes are those where aryl substituents (phenyl and 4-methoxyphenyl-) were introduced at the α-position to the amide (Scheme 4e). In these cases, the cyclopropyl moiety remained intact, while oxazine **8** and oxazoline **9**[22] were formed. This difference likely arises from oxidation of the aryl group rather than the cyclopropyl group in these substrates, as electron-neutral and -rich aryl groups are susceptible to single-electron oxidation under electrochemical conditions.[25] CV experiments on both substrates further supported that the aryl ring is more readily oxidized compared to the cyclopropane ring (Figure S4). These findings corroborate with our proposed oxidation mechanism for cyclopropane in this strain-release protocol; when the cyclopropane is not oxidized, as observed here, it remains intact.

Moving forward, we aimed to extend our strain-release skeletal rearrangement approach to cyclobutane ring, given its comparable ring strain to cyclopropane. Drawing insights from mechanistic studies on cyclopropane substrates, we opted to theoretically predict the reactivity of cyclobutane substrates (Scheme 4f). Using the same DFT methods, spin population analysis of **10a** indicated that the amidyl radical cation is the lowest energy species in this scenario. Additionally, DFT calculations revealed that the free energy barrier for the cyclization step of the radical cation with **10a** is 10.4 kcal·mol^{-1}, with a reaction rate of 10^5 s^{-1}. Considering the computational data obtained for cyclopropane substrates (Scheme 4a), these findings strongly suggest that the cyclobutyl substrate is not feasible within our protocol. However, upon introducing a methyl substituent at the α-position of the cyclobutane moiety (**10b**), the lowest energy spin population now corresponded to the cyclobutyl radical cation, and the free energy barrier for the cyclization step of the radical cation decreased to 3.3 kcal·mol^{-1}, with a reaction rate of 10^{10} s^{-1}, indicating potential strain-release reactivity of this cyclobutane substrate.

Extension to cyclobutanes. Following theoretical predictions, experimental studies were conducted (Scheme 5) to validate the proposed reactivity of cyclobutane substrates. As expected, cyclobutylmethyl benzamide (**10a**) displayed no reactivity under standard conditions, with all starting material recovered. In stark contrast, when *N*-((1-methylcyclobutyl)methyl)benzamide (**10b**) was subjected to the same conditions, although no isolatable product was obtained, a noticeable consumption of **10b** was observed. This led us to speculate that the alkyl carbon radical generated by the ring opening of **10b** might be overly reactive, resulting in a series of side reactions. Building upon this hypothesis, we implemented a strategy to capture these alkyl carbon radicals using oxygen. Surprisingly, this approach yielded 5-cyclopropyl-5-methyl-2-phenyl-4,5-dihydrooxazole (**11b**) in 52% yield. In contrast, **10a** remained unreactive even under an oxygen atmosphere, with a significant amount of starting material recovered, aligning with our theoretical predictions. Remarkably, the transformation of **10b** to **11b** highlights the capability of electrochemical synthesis to generate cyclopropanes from cyclobutanes, representing a novel finding heretofore unreported. Further exploration of the oxidative skeletal rearrangement of cyclobutane revealed that the reaction proceeded well in the presence of various functional substituents and multiple substituents on the arene, yielding the corresponding products in moderate to good yields.



Scheme 5. Substrate scope of *N*-(1-methylcyclobutyl)methyl aryl amide. [a] Standard conditions: amide **10** (0.2 mmol, 1 equiv), nBu_4NBF_4 (0.5 mmol), CH_3CN (5 mL, bubble oxygen for 1 hour in advance), C (graphite) anode, Pt (platinum) cathode (current intensity = 3.3 mA/cm^2), r.t. and i = 5 mA, undivided cell; Isolated yields. [b] Yield in parenthesis represents the yield of recovered starting materials.

Proposed mechanisms. Plausible mechanisms for the electrochemical strain-release skeletal rearrangement of cyclopropanes and cyclobutanes with pendant amide groups were proposed in Scheme 6, integrating both theoretical and experimental findings. Under electrocatalysis, the anodic oxidation of the cyclopropane and cyclobutane moiety in substrates **1b** and **10b** generates the corresponding radical cation **I**. Subsequent intramolecular cyclization facilitated by the amide group, forms radical **II** (from cyclopropanes) and **II′** (from cyclobutanes). Radical **II** undergoes further oxidation at the anode, resulting in cation **III**, followed by deprotonation to yield oxazoline **2b**. On the other hand, the highly reactive radical **II′** captures oxygen to form peroxy radical **III′**, which initiates a 1,5-hydrogen atom transfer (HAT) process, leading to the formation of a more stable secondary carbon radical (**IV′**). Subsequently, radical **IV′** participates in a substitution to form the cyclopropyl ring **11b**,

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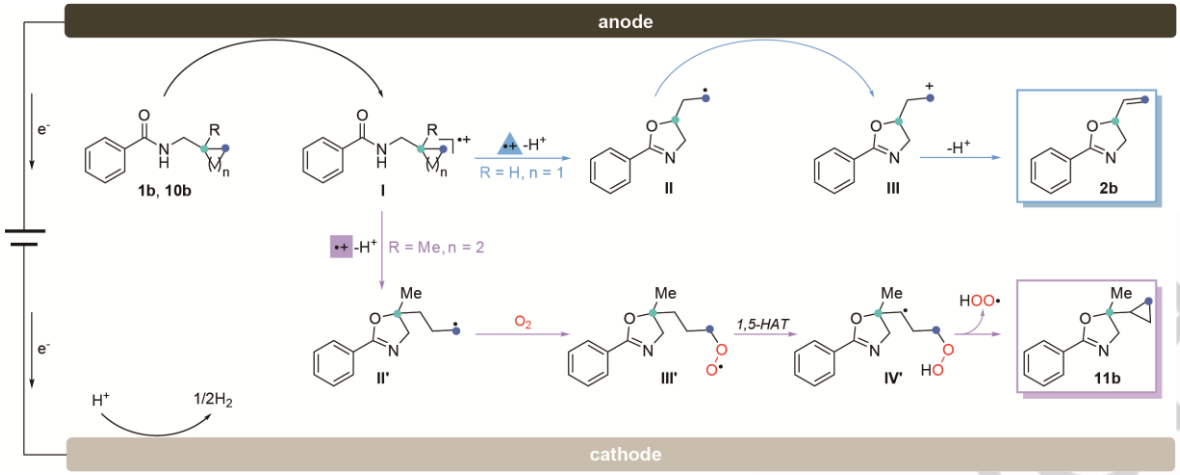
concurrently releasing a hydrogen peroxide radical.[26] Meanwhile, the protons released during these processes are reduced at the cathode, culminating the production of hydrogen gas.



Scheme 6. Proposed mechanisms.

Conclusion

In conclusion, our investigation of strain-release-driven electrochemical reactions has introduced a convenient method for direct oxidation of non-activated cyclopropanes. This innovative approach not only facilitates the synthesis of diverse oxazolines and oxazines but also validates the feasibility of cyclopropane ring cleavage in *N*-cyclopropylmethyl/ethyl amides under electrochemical conditions. Moreover, comprehensive mechanistic and theoretical investigations have provided profound insights into the reaction mechanisms and the key intermediates involved. These investigations also guided us to extend the protocol to cyclobutanes based on theoretical predictions, leading to expansion of our protocol to the oxidation of *N*-((1-methylcyclobutyl)methyl) amides for the construction of oxazolines with cyclopropane substituents through similar strain-release mechanisms. Such mechanistic studies not only deepen our understanding of the underlying chemical processes but also establish a solid foundation for the design, optimization, and prediction of future electrochemical transformations. Our work thus opens avenues for synthesizing oxazolines and oxazines, and acts as a proof of concept, demonstrating the feasibility of strain-release-driven ring opening in non-activated cyclopropanes and cyclobutanes under electrochemical conditions.

Acknowledgements

We are grateful for the financial support provided by Pfizer (A-0008361-00-00), the Agency for Science, and the Prime Minister's Office of Singapore under its NRF-CRP Programme (NRF-CRP27-2021-0001).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: electrochemical synthesis, rearrangement, small ring systems, strained molecules, synthetic methods

[1] aA. Baeyer, *Berichte der deutschen chemischen Gesellschaft* **1885**, *18*, 2269-2281; bK. B. Wiberg, *Angewandte Chemie International Edition in English* **1986**, *25*, 312-322; cI. V. Komarov, *Russ. Chem. Rev.* **2001**, *70*, 991-1016; dA. de Meijere, S. I. Kozhushkov, H. Schill, *Chem. Rev.* **2006**, *106*, 4926-4996; eM. R. Wilson, R. E. Taylor, *Angew. Chem. Int. Ed.* **2013**, *52*, 4078-4087; fP. Wipf, E. M. Skoda, A. Mann, in *The Practice of Medicinal Chemistry (Fourth Edition)* (Eds.: C. G. Wermuth, D. Aldous, P. Raboisson, D. Rognan), Academic Press, San Diego, **2015**, pp. 279-299.

[2] aM. D. Levin, P. Kaszynski, J. Michl, *Chem. Rev.* **2000**, *100*, 169-234; bE. W. Delia, I. J. Lochert, *Org. Prep. Proced. Int.* **1996**, *28*, 411-441; cR. Bartnik, A. P. Marchand, *Synlett* **1997**, *1997*, 1029-1039; dC. Jamieson, J. C. Walton, K. U. Ingold, *Journal of the Chemical Society, Perkin Transactions 2* **1980**, 1366-1371; eK. B. Wiberg, S. T. Waddell, *J. Am. Chem. Soc.* **1990**, *112*, 2194-2216.

[3] J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 3209-3226.

[4] R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, *351*, 241-246.

[5] R. Gianatassio, D. Kadish, *Org. Lett.* **2019**, *21*, 2060-2063.

[6] M. Ociepa, A. J. Wierzba, J. Turkowska, D. Gryko, *J. Am. Chem. Soc.* **2020**, *142*, 5355-5361.

[7] V. Šunjić, V. Petrović Peroković, in *Organic Chemistry from Retrosynthesis to Asymmetric Synthesis* (Eds.: V. Šunjić, V. Petrović Peroković), Springer International Publishing, Cham, **2016**, pp. 173-188.

[8] X.-L. Jiang, Q. Liu, K.-F. Wei, T.-T. Zhang, G. Ma, X.-H. Zhu, G.-X. Ru, L. Liu, L.-R. Hu, W.-B. Shen, *Communications Chemistry* **2023**, *6*, 35.

[9] C. Li, Y. Zeng, H. Zhang, J. Feng, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2010**, *49*, 6413-6417.

10.1002/anie.202413723

[10] B.-C. Hong, S.-H. Chen, E. S. Kumar, G.-H. Lee, K.-J. Lin, *J. Chin. Chem. Soc. (Taipei, Taiwan)* **2003**, *50*, 917-926.

[11] aH.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151-1196; bM. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321-347; cT. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504-5523; dH. Ding, X.-L. Zhang, A. Guo, Q. P. Lee, C. Cai, M. Li, H. Cao, X.-W. Liu, *J. Am. Chem. Soc.* **2024**.

[12] aG. Fumagalli, S. Stanton, J. F. Bower, *Chem. Rev.* **2017**, *117*, 9404-9432; bL. Souillart, N. Cramer, *Chem. Rev.* **2015**, *115*, 9410-9464; cP.-h. Chen, B. A. Billett, T. Tsukamoto, G. Dong, *ACS Catalysis* **2017**, *7*, 1340-1360.

[13] aS. Danishefsky, *Acc. Chem. Res.* **1979**, *12*, 66-72; bJ. B. Lambert, J. J. Napoli, K. K. Johnson, K. N. Taba, *The Journal of Organic Chemistry* **1985**, *50*, 1291-1295; cJ. G. M. Morton, M. A. Dureen, D. W. Stephan, *Chem. Commun.* **2010**, *46*, 8947-8949; dC. Rösner, U. Hennecke, *Org. Lett.* **2015**, *17*, 3226-3229; eS. M. Banik, K. M. Mennie, E. N. Jacobsen, *J. Am. Chem. Soc.* **2017**, *139*, 9152-9155; fN. O. Ilchenko, M. Hedberg, K. J. Szabó, *Chemical Science* **2017**, *8*, 1056-1061; gD. Wang, X.-S. Xue, K. N. Houk, Z. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 16861-16865; hZ.-Y. Zhang, Z.-Y. Liu, R.-T. Guo, Y.-Q. Zhao, X. Li, X.-C. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 4028-4032.

[14] J. Liu, L. Lu, D. Wood, S. Lin, *ACS Central Science* **2020**, *6*, 1317-1340.

[15] Z. Zuo, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.* **2021**, *60*, 25252-25257.

[16] aS. Kolb, M. Petzold, F. Brandt, P. G. Jones, C. R. Jacob, D. B. Werz, *Angew. Chem. Int. Ed.* **2021**, *60*, 15928-15934; bS. Kolb, N. L. Ahlburg, D. B. Werz, *Org. Lett.* **2021**, *23*, 5549-5553.

[17] aL. Ge, C. Zhang, C. Pan, D.-X. Wang, D.-Y. Liu, Z.-Q. Li, P. Shen, L. Tian, C. Feng, *Nat. Commun.* **2022**, *13*, 5938; bP. Peng, X. Yan, K. Zhang, Z. Liu, L. Zeng, Y. Chen, H. Zhang, A. Lei, *Nat. Commun.* **2021**, *12*, 3075.

[18] aM. Iyoda, *Adv. Synth. Catal.* **2009**, *351*, 984-998; bM. K. Tse, S. Bhor, M. Klawonn, G. Anilkumar, H. Jiao, C. Döbler, A. Spannenberg, W. Mägerlein, H. Hugl, M. Beller, *Chemistry – A European Journal* **2006**, *12*, 1855-1874.

[19] J. A. Shapiro, T. A. Wencewicz, *Metallomics* **2017**, *9*, 463-470.

[20] Y. Sevgiler, E. Ö. Oruç, N. Üner, *Pestic. Biochem. Physiol.* **2004**, *78*, 1-8.

[21] R. Hoogenboom, *Angew. Chem. Int. Ed.* **2009**, *48*, 7978-7994.

[22] Deposition numbers 2340345 (for **2m**) and 2340337 (for **9**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[23] M. Balandeh, C. Waldmann, D. Shirazi, A. Gomez, A. Rios, N. Allison, A. Khan, S. Sadeghi, *J. Electrochem. Soc.* **2017**, *164*, G99.

[24] M. Darzina, A. Jirgensons, *Org. Lett.* **2024**, *26*, 2158-2162.

[25] aH. Yu, M. Jiao, R. Huang, X. Fang, *Eur. J. Org. Chem.* **2019**, *2019*, 2004-2009; bS. Strekalova, A. Kononov, V. Morozov, O. Babaeva, E. Gavrilova, Y. Budnikova, *Adv. Synth. Catal.* **2023**, *365*, 3375-3381.

[26] D. P. Poudel, A. Pokhrel, R. K. Tak, M. Shankar, R. Giri, *Science* **2023**, *381*, 545-553.

10.1002/anie.202413723

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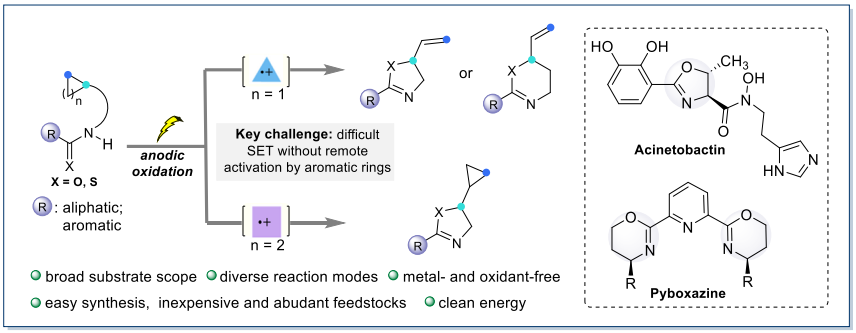

Strain-release-driven reactions represent a powerful strategy to access a diverse array of chemical scaffolds. The direct activation of alkyl non-biased cyclopropanes and cyclobutanes through electrochemical oxidation facilitates the formation of a wide range of oxazoline and oxazine derivatives, offering crucial insights into the oxidation of small cycloalkane rings.