

## EDGE ARTICLE

Cite this: *Chem. Sci.*, 2020, 11, 5313

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# Synthesis of unstrained Criegee intermediates: inverse $\alpha$ -effect and other protective stereoelectronic forces can stop Baeyer–Villiger rearrangement of $\gamma$ -hydroperoxy- $\gamma$ -peroxylactones†

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*How far can we push the limits in removing stereoelectronic protection from an unstable intermediate? We address this question by exploring the interplay between the primary and secondary stereoelectronic effects in the Baeyer–Villiger (BV) rearrangement by experimental and computational studies of  $\gamma$ -OR-substituted  $\gamma$ -peroxylactones, the previously elusive non-strained Criegee intermediates (CI). These new cyclic peroxides were synthesized by the peroxidation of  $\gamma$ -ketoesters followed by *in situ* cyclization using a  $\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{H}_2\text{O}_2$  system. Although the primary effect (alignment of the migrating C–R<sub>m</sub> bond with the breaking O–O bond) is active in the 6-membered ring, weakening of the secondary effect (donation from the OR lone pair to the breaking C–R<sub>m</sub> bond) provides sufficient kinetic stabilization to allow the formation and isolation of stable  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactones with a methyl-substituent in the C6-position. Furthermore, supplementary protection is also provided by reactant stabilization originating from two new stereoelectronic factors, both identified and quantified for the first time in the present work. First, an unexpected boat preference in the  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactones weakens the primary stereoelectronic effects and introduces a  $\sim 2$  kcal mol<sup>-1</sup> Curtin–Hammett penalty for reacquiring the more reactive chair conformation. Second, activation of the secondary stereoelectronic effect in the TS comes with a  $\sim 2$ – $3$  kcal mol<sup>-1</sup> penalty for giving up the exo-anomeric stabilization in the 6-membered Criegee intermediate. Together, the three new stereoelectronic factors (inverse  $\alpha$ -effect, misalignment of reacting bonds in the boat conformation, and the exo-anomeric effect) illustrate the richness of stereoelectronic patterns in peroxide chemistry and provide experimentally significant kinetic stabilization to this new class of bisperoxides. Furthermore, mild reduction of  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactone with  $\text{Ph}_3\text{P}$  produced an isolable  $\gamma$ -hydroxy- $\gamma$ -peroxylactone, the first example of a structurally unencumbered CI where neither the primary nor the secondary stereoelectronic effect are impeded. Although this compound is relatively unstable, it does not undergo the BV reaction and instead follows a new mode of reactivity for the CI – a ring-opening process.*

Received 20th February 2020  
Accepted 5th May 2020

DOI: 10.1039/d0sc01025a

rsc.li/chemical-science

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† Electronic supplementary information (ESI) available. CCDC 1980721. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc01025a

## Introduction

The Baeyer–Villiger (BV) reaction was discovered by Adolf von Baeyer and Victor Villiger in 1899, more than one hundred and twenty years ago.<sup>1,2</sup> This oxidative transformation opens synthetic access to an ester from a ketone or to a lactone from a cyclic ketone, using peroxyacids as an oxidant.<sup>3</sup> Thousands of studies are devoted to this reaction<sup>4–8</sup> and its regio- and stereoselective versions were developed.<sup>9–12</sup> An important monomer for polyesters and polyamides – caprolactone is produced *via* BV reaction in industry.<sup>13,14</sup> Throughout its history, several mechanisms were suggested for the BV oxidation.<sup>15,16</sup> Presently, a mechanism passing through a tetrahedral Criegee



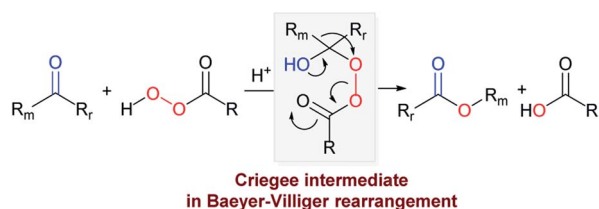
intermediate (CI) is generally accepted (Scheme 1).<sup>17–20</sup> Surprisingly, this intermediate has not been structurally characterized until our initial report.<sup>21</sup> Only three partially characterized examples of “protected” CIs have been known at that point.<sup>22–24</sup>

The hydroxyl peroxyesters, Criegee intermediates of the BV rearrangement, remained elusive due to their high reactivity (Scheme 1).<sup>25</sup> However, the key to understanding the BV rearrangement mechanism and to the design a stereo- and regio-selective BV processes lies in the intimate details of the CI structure, a notion that provides motivation for this research.

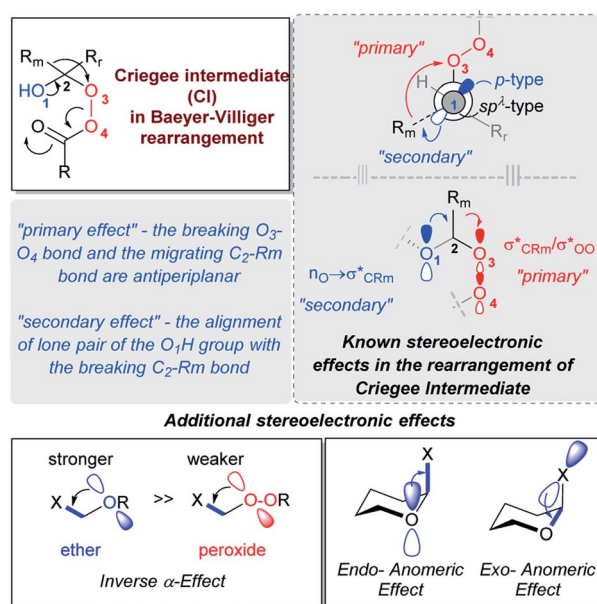
An additional broader incentive behind this work is to expand conceptual understanding of chemistry of organic peroxides. In comparison to the textbook organic oxygen-containing functionalities, for which the vast body of chemical knowledge has been accumulated, it is often impossible to predict whether a suggested organic peroxide would have more than fleeting stability. Because the experimental data for this neglected O-containing functionality is still relatively scarce, computational analysis becomes essential for evaluating synthetic routes to the new classes of organic peroxides and for advancing conceptual understanding of their structure and reactivity. Our work continues to underscore the utility of stereoelectronic thinking as the bridge between experimental data and understanding and predicting organic peroxide chemistry. Herein, we will show that the classic repertoire of stereoelectronic effects in the BV reaction is incomplete and that, in addition to two classic stereoelectronic effects that facilitate BV by activating CIs, there are also effects that prevent BV by protecting and/or stabilizing CIs. Two of such effects are quantified for the first time in the present work.

The assistance of two stereoelectronic effects is well-documented in the transformation of the Criegee intermediates into the final BV product.<sup>26–29</sup> The key participants of these effects are the p-type lone pair of O<sub>1</sub>, the breaking C<sub>2</sub>–R<sub>m</sub> bond and the O<sub>3</sub>–O<sub>4</sub> acceptor (Scheme 2). The “primary stereoelectronic effect” requires that the breaking O–O bond and the migrating C<sub>2</sub>–R<sub>m</sub> bond are antiperiplanar.<sup>30</sup> The “secondary effect” is operative when the lone pair of the O<sub>1</sub>H group aligns with the breaking C<sub>2</sub>–R<sub>m</sub> bond.<sup>31,32</sup> When both effects take place, an uninterrupted electron flow from the donor (O<sub>1</sub>) to the acceptor assures that donation from the O<sub>1</sub> lone pair assists in breaking the C<sub>2</sub>–R<sub>m</sub> bond by stabilizing the incipient cationic center as the R<sub>m</sub> group moves to O<sub>3</sub> and the O<sub>3</sub>O<sub>4</sub> bond breaks. As the result, the O<sub>1</sub>=C<sub>2</sub> and R<sub>m</sub>–O<sub>3</sub> bonds are formed.

In our initial report of a stable Criegee intermediates, we have built two “stereoelectronic traps” by selective

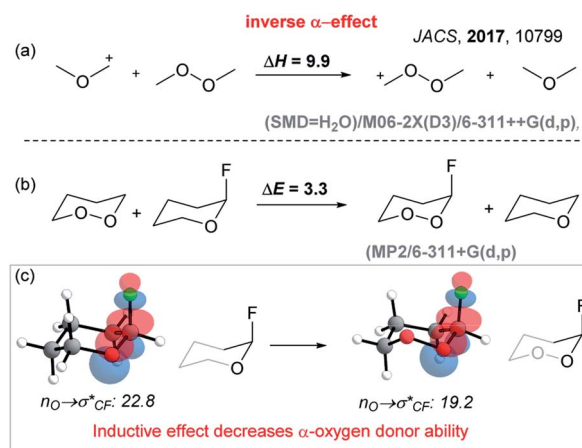


Scheme 1 Postulated mechanism of Baeyer–Villiger oxidation.



Scheme 2 The toolbox of stereoelectronic effects related to the BV of Criegee intermediate.

deactivation of these classic stereoelectronic effects (Scheme 2).<sup>21</sup> The “first stereoelectronic trap” increased the stability of CI by constraining it in a five-membered cycle with the goal of preventing antiperiplanarity of the breaking O<sub>3</sub>–O<sub>4</sub> bond and the migrating C<sub>2</sub>–R<sub>m</sub> bond.<sup>26,33</sup> The “second stereoelectronic trap” weakens the donation of electron density from a lone pair of the O<sub>1</sub>H group to the breaking C<sub>2</sub>–R<sub>m</sub> bond. We disclosed that this is achieved *via* the replacement of the O<sub>1</sub>H group by the O<sub>1</sub>OH group. The change activates the “inverse  $\alpha$ -effect”,<sup>34</sup> a new stereoelectronic effect introduced previously for the control of CI stability. This recently discovered effect accounts for the lower donor ability of peroxides in intramolecular hyperconjugative interactions with the adjacent acceptors.<sup>35</sup>



Scheme 3 The magnitude of inverse  $\alpha$ -effect in carbenium ions (a) and anomeric systems (b). Comparison of NBO  $n_{\text{O}} \rightarrow \sigma_{\text{C-F}}^*$  interactions (c) (energies are in kcal mol<sup>−1</sup>).

The essence of inverse  $\alpha$ -effect is shown in the Scheme 3, which illustrates that the two oxygen atoms of a peroxide moiety do not stabilize an adjacent cationic center or a stereo-electronically aligned  $\sigma$ -acceptor as much as a single oxygen atom of an ether. This effect has the potential to unlock many unusual aspects of peroxide chemistry.<sup>34</sup> For example, it can impose  $\sim 10$  kcal mol<sup>-1</sup> penalty for the generation of simple peroxy-carbenium ions relative to their oxocarbenium analogues. The power and broad utility of inverse  $\alpha$ -effect in peroxide chemistry was illustrated by using it to discover previously invisible chemistry of peroxy-carbenium cations,<sup>36</sup> and to understand the paradoxical situations where a peroxide is more stable than its mono-oxygen counterpart.<sup>21</sup>

Five-membered peroxy-Criegee intermediates ( $\beta$ -hydroperoxy- $\beta$ -peroxylactones) were protected from Baeyer-Villiger rearrangement by disrupting *both* stereoelectronic effects in BV by (a) breaking antiperiplanarity of O<sub>3</sub>-O<sub>4</sub> and C<sub>2</sub>-R<sub>m</sub> bond by cycle formation, and by (b) lowering donor ability of O<sub>1</sub> atom in O<sub>1</sub>OH group by inverse  $\alpha$ -effect (Scheme 4).<sup>21</sup> However, the protection in  $\beta$ -hydroxy- $\beta$ -peroxylactones (five-

membered Criegee intermediates) was provided mostly by deactivation of the primary stereoelectronic effect (Scheme 4).<sup>21</sup>

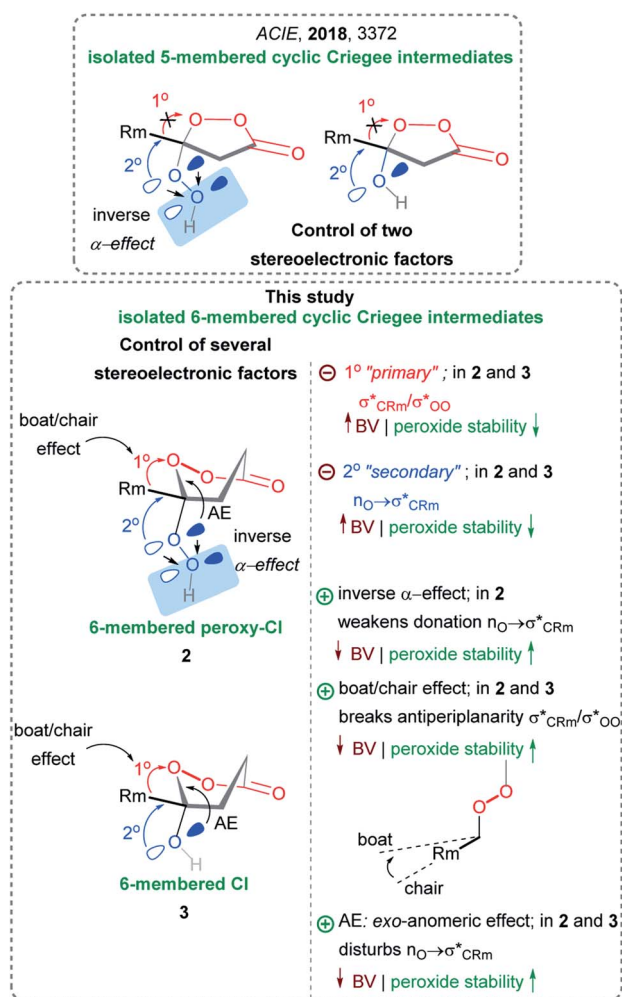
In the present work, we remove another level of protective armor by restoring the unstrained 6-membered cycle for reactivating the primary stereoelectronic effect as an assistant to BV rearrangement. Our goal herein is to determine if attenuation of the secondary stereoelectronic effect alone can also save the Criegee intermediate from following the BV reaction (Scheme 4). We have introduced this protection by weakening the donor ability of the O<sub>1</sub> atom in the six-membered CIs *via* the inverse  $\alpha$ -effect. Furthermore, we will illustrate that even the combination of the three aforementioned effects was incomplete and that exo-anomeric effect is the fourth kinetically significant component of this system of intertwined stereoelectronic effects. Finally, we will also identify a new way to control the "primary stereoelectronic effect" with the boat/chair conformational transition in the six-membered cyclic peroxides.

In addition to providing a deeper insight into the key intermediate of the BV reaction, the goal of this work is to develop an approach to a previously unavailable class of organic peroxides. The recent renaissance in chemistry of organic peroxides has catalyzed the discovery of antimalarial (*e.g.*, artemisinin),<sup>37-45</sup> anticancer,<sup>46-48</sup> anthelmintic,<sup>49-51</sup> antiviral<sup>52-54</sup> and antimicrobial<sup>55-59</sup> peroxides (in addition to the traditional applications as precursors,<sup>3</sup> oxidizers,<sup>60-63</sup> polymerization initiators, vulcanizing agents,<sup>64-66</sup> and explosives).<sup>67</sup> Despite the long history of peroxide chemistry, their selective synthesis and the inaccessibility of certain classes of peroxides remains a fundamental problem.<sup>68-70</sup>

Based on our earlier findings, we designed new methods for synthesis of stable 5-membered cyclic Criegee intermediates ( $\beta$ -hydroxy- $\beta$ -peroxylactones),<sup>21</sup> hydroperoxy-analogs of Criegee intermediates ( $\beta$ -hydroperoxy- $\beta$ -peroxylactones),<sup>71</sup> and alkoxy-analogs of Criegee intermediates ( $\beta$ -alkoxy- $\beta$ -peroxylactones)<sup>36</sup> (Scheme 4). The new insights in the nature of factors controlling the stability of the  $\gamma$ -hydroxy- $\gamma$ -peroxylactone core in the new Criegee intermediates allowed us to design a synthetic approach to  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactones, a novel class of organic peroxides (Scheme 4). It should be noted that the 6-membered  $\gamma$ -hydroxy- $\gamma$ -peroxylactones were postulated earlier to be unstable and highly reactive.<sup>33,72</sup>

## Results and discussion

Even in the absence of a  $\gamma$ -hydroxy or  $\gamma$ -hydroperoxy groups, synthetic access to  $\gamma$ -peroxylactones is relatively difficult. The known approaches to these compounds, such as a peroxidation of  $\gamma$ -hydroxy amides,<sup>73,74</sup> lactones,<sup>75,76</sup> and  $\gamma$ -hydroxy esters,<sup>77</sup> ozonolysis<sup>78</sup> or singlet oxygen treatment<sup>79</sup> of allylic esters, and few scattered examples,<sup>80-83</sup> have limited utility. In contrast, the combination of dicarbonyl compounds and hydrogen peroxide as starting materials benefits from simplicity and affordability. In this paper, we disclose how these simple conditions can be used for peroxidation of  $\gamma$ -ketoesters with *in situ* cyclization into  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactones.



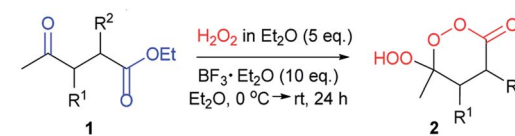
Scheme 4 Fine-tuning the stability of Criegee intermediates *via* construction and partial deactivation of stereoelectronic traps. Arrows – the effect is activated. Crossed out arrows – the effect is deactivated.

In the initial screening step, we studied the reaction of ethyl-3-benzyl-4-oxopentanoate (**1a**) with H<sub>2</sub>O<sub>2</sub> in the presence of various acids and solvents (Table 1).

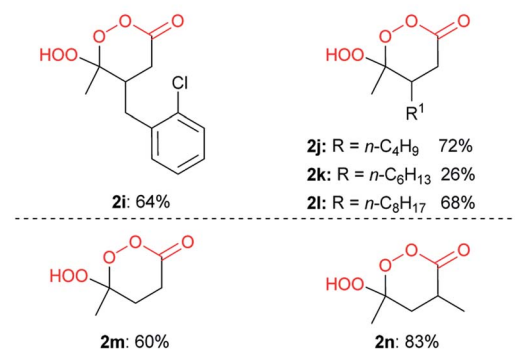
We began our study with the use of 10 eq. of an ethereal solution of H<sub>2</sub>O<sub>2</sub> and 10 eq. of BF<sub>3</sub>·Et<sub>2</sub>O (Table 1, entry 1) according to previously optimized conditions for β-hydroperoxy-β-peroxylactone synthesis.<sup>24,71</sup> Yield of γ-hydroperoxy-γ-peroxylactone **2a** was 54% (Table 1, entry 1). Attempts to use other Lewis and Brønsted acids were counterproductive, the yield of **2a** decreased to 13–46% (Table 1, entries 2–6). Decreasing the amount of BF<sub>3</sub>·Et<sub>2</sub>O led to decreasing the yield of **2a** to 19% (Table 1, entries 7, 8). Substitution of diethyl ether to acetonitrile yields target peroxide **2a** in moderate yield (Table 1, entry 9). Using less H<sub>2</sub>O<sub>2</sub> (5 eq. and 3 eq. in entries 10, 11) results in the formation of peroxide **2a** in 53% and 27% yield, respectively.

With optimized conditions in hand (Table 1, entry 10) we investigated the influence of substituents in the C2 and C3 positions of starting γ-ketoesters **1** on the outcome of the peroxidation reaction (Scheme 5).

As shown in Scheme 5, a range of 1,4-ketoesters **1a–l**, with various R<sup>1</sup> substituent – electron-donating and electron-withdrawing groups in aryl ring of benzyl substitutes **1a–i** and alkyl groups **1j–l**, were viable in the peroxidation reaction, γ-hydroperoxy-γ-peroxylactones **2a–l** were obtained with from moderate (44%, **2d**) to good (72%, **2j**) yields. The exception is a hexyl substituted γ-ketoester **1k** where the yield of γ-hydroperoxy-γ-peroxylactone **2k** is 26%. Unsubstituted and C4-methyl-substituted γ-hydroperoxy-γ-peroxylactones **2m**



|                                 |     |                                 |     |                                  |     |
|---------------------------------|-----|---------------------------------|-----|----------------------------------|-----|
| <b>2a</b> : R = H               | 53% | <b>2d</b> : R = Br              | 44% | <b>2g</b> : R = CH <sub>3</sub>  | 71% |
| <b>2b</b> : R = NO <sub>2</sub> | 56% | <b>2e</b> : R = <i>t</i> -Bu    | 67% | <b>2h</b> : R = OCH <sub>3</sub> | 62% |
| <b>2c</b> : R = Cl              | 47% | <b>2f</b> : R = CH <sub>3</sub> | 64% |                                  |     |



Scheme 5 Scope of γ-hydroperoxy-γ-peroxylactones **2** synthesized from γ-ketoesters **1**.

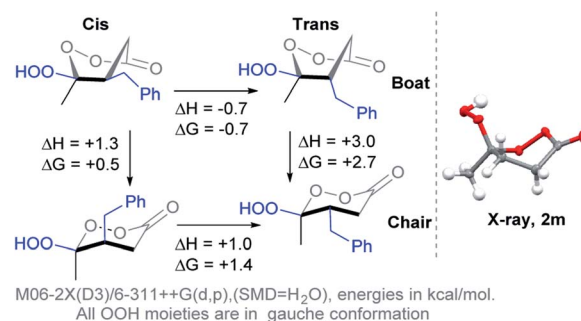
Table 1 Screening conditions for γ-hydroperoxy-γ-peroxylactone **2a** synthesis<sup>a</sup>

| Entry          | Eq. H <sub>2</sub> O <sub>2</sub> | Acid, eq.                              | Yield <b>2a</b> , % |
|----------------|-----------------------------------|--|---------------------|
| 1              | 10                                | BF <sub>3</sub> ·Et <sub>2</sub> O, 10 | 54                  |
| 2              | 10                                | SnCl <sub>4</sub> , 5                  | 46                  |
| 3              | 10                                | HClO <sub>4</sub> , 10                 | 13                  |
| 4              | 10                                | HBf <sub>4</sub> , 10                  | 17                  |
| 5              | 10                                | TsOH·H <sub>2</sub> O, 10              | 24                  |
| 6              | 10                                | PMA, 1                                 | 15                  |
| 7              | 10                                | BF <sub>3</sub> ·Et <sub>2</sub> O, 5  | 38                  |
| 8              | 10                                | BF <sub>3</sub> ·Et <sub>2</sub> O, 2  | 19                  |
| 9 <sup>b</sup> | 10                                | BF <sub>3</sub> ·Et <sub>2</sub> O, 10 | 35                  |
| 10             | 5                                 | BF <sub>3</sub> ·Et <sub>2</sub> O, 10 | 53                  |
| 11             | 3                                 | BF <sub>3</sub> ·Et <sub>2</sub> O, 10 | 27                  |

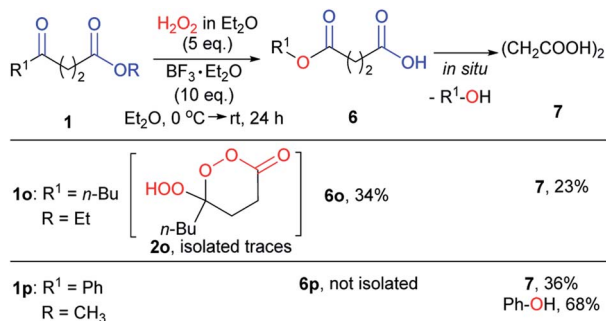
<sup>a</sup> General procedure: an ethereal solution of H<sub>2</sub>O<sub>2</sub> (4.30 M, 0.698–2.326 mL, 3.0–10.0 mmol, 3.0–10.0 eq.) was added with stirring to a solution of **1a** (234.3 mg, 1.00 mmol, 1.0 eq.) in Et<sub>2</sub>O (3.5 mL). The mixture was cooled to 0 °C and acid was added dropwise with stirring. The reaction mixture was then stirred at 20–25 °C for 24 h. <sup>b</sup> CH<sub>3</sub>CN as solvent.

and **2n** were synthesized in good yields, 60%, and 83%, respectively.

The γ-hydroperoxy-γ-peroxylactones **2a–l** are produced as a mixture of two diastereomers with the predominance of the *trans* isomer. For example, the peroxylactone **2a** was formed in the 22 : 78 *cis* : *trans* ratio (see ESI<sup>†</sup>). This finding disagreed with the greater calculated thermodynamic stability of the *cis* isomer of **2a** in the chair conformation (1.4 kcal mol<sup>-1</sup>, Scheme 6). This discrepancy led us to explore conformational behavior of this system deeper. Surprisingly, calculations revealed that both diastereomers prefer the boat conformation where the *trans*-conformer is 0.7 kcal mol<sup>-1</sup> more stable in a full agreement with the experimental data. Furthermore, the boat



Scheme 6 Relative stability of the four forms of γ-hydroperoxy-γ-peroxylactone **2**.

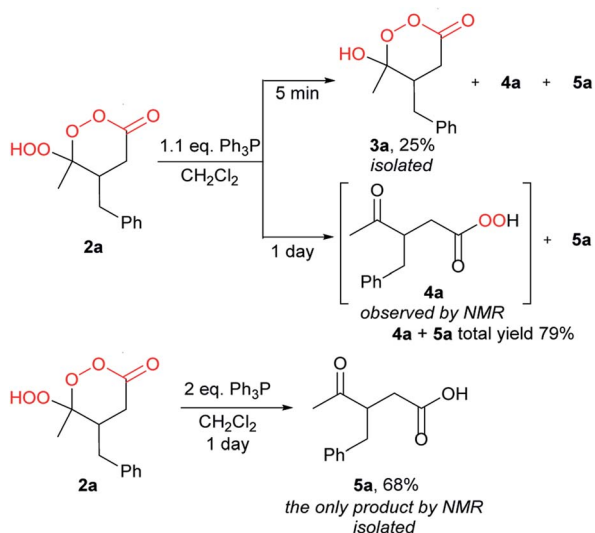


Scheme 7 Transformation of  $\gamma$ -ketoesters with primarily alkyl or phenyl substituent in C4 position **1o**, **1p** in optimal conditions.

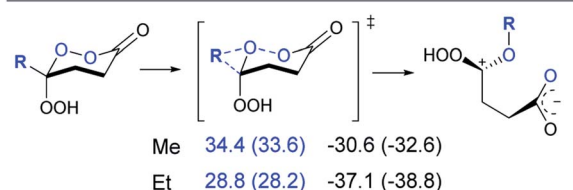
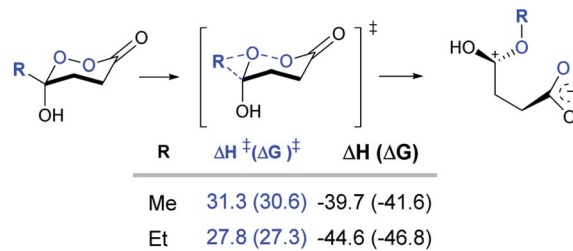
conformation was found in the X-ray structure of related peroxy lactone **2m** (Scheme 6). This finding will have significant stereoelectronic consequences for our subsequent mechanistic discussions.

When the substituent at the C4 position of  $\gamma$ -ketoesters is either a primary alkyl or the phenyl group (**1o**, **1p**), the corresponding  $\gamma$ -peroxylactones were not obtained. For these substrates, the observed reaction products **6** and **7** result from the Baeyer–Villiger rearrangement and subsequent hydrolysis (Scheme 7).

Interesting results were obtained by treatment of  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactone **2a** with  $\text{Ph}_3\text{P}$  (Scheme 8). The reaction of **2a** with 1.1 eq.  $\text{Ph}_3\text{P}$  for 5 min followed by chromatographic purification resulted in quite unstable  $\gamma$ -hydroxy- $\gamma$ -peroxylactone **3a** in 25% yield, the remaining reaction mass was a mixture of  $\gamma$ -ketoacid **5a** and a new compound that we tentatively assign the structure of  $\gamma$ -ketoperacid **4a** (see the ESI<sup>†</sup>). Previously, the  $\gamma$ -hydroxy- $\gamma$ -peroxylactone was considered to be non-isolable due to the preferred Baeyer–Villiger rearrangement.<sup>33,72</sup> The reaction of **2a** with 1.1 eq.  $\text{Ph}_3\text{P}$  for 1 day gave only a mixture of the ring-opened products **5a** and **4a**, according to NMR analysis (see ESI<sup>†</sup>). The treatment of  $\gamma$ -



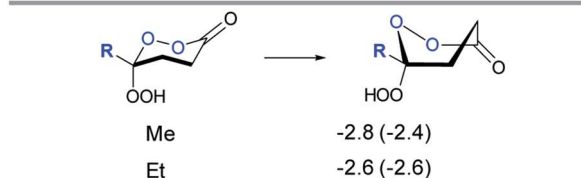
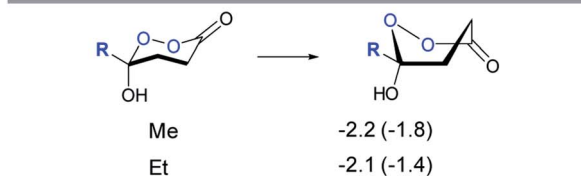
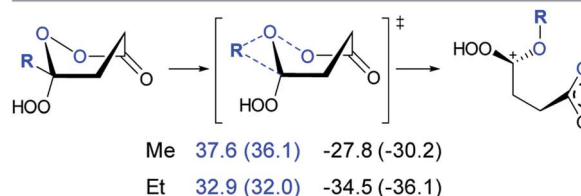
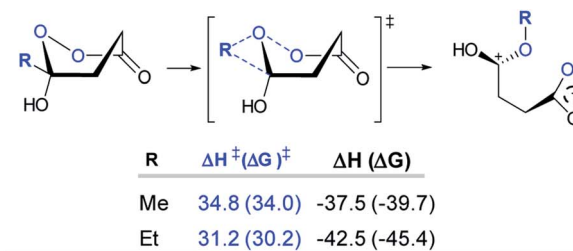
Scheme 8 Reduction of  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactone **2a**.



(SMD=H<sub>2</sub>O) M06-2X(D3)/6-311++G(d,p), Energies in kcal/mol

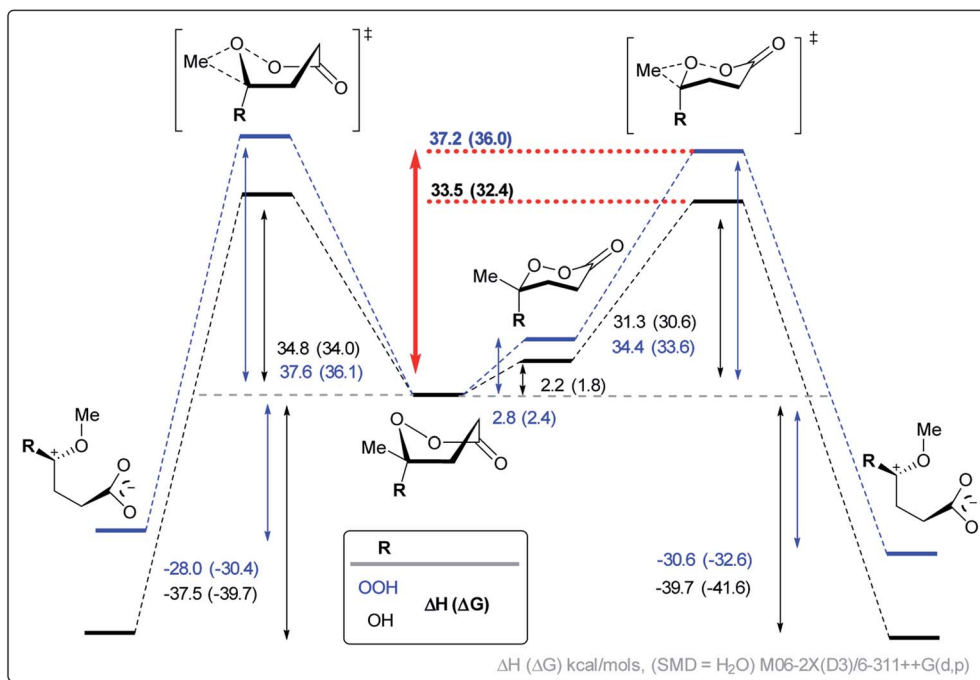
Scheme 9 Computational analysis of the BV 1,2-shift in cyclic Cls and their hydroperoxyl analogs for the chair conformations.

hydroperoxy- $\gamma$ -peroxylactone **2a** by 2.0 eq.  $\text{Ph}_3\text{P}$  leads to the formation of  $\gamma$ -ketoacid **5a** as the only product by NMR (68% isolated yield, Scheme 8). Thus,  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactone under the reductive conditions prefers C–O scission that leads to the peroxide ring opening rather than to Baeyer–Villiger



(SMD=H<sub>2</sub>O) M06-2X(D3)/6-311++G(d,p), Energies in kcal/mol

Scheme 10 Computational analysis of the BV 1,2-shift in cyclic Cls and their hydroperoxyl analogs for the boat conformations.



Scheme 11 Computational analysis of the BV 1,2-shift in cyclic CIs and their hydroperoxy analogs for the boat and chair conformations.

rearrangement. The products of Baeyer–Villiger rearrangement were not observed in all cases.

### Computational analysis

As the starting point, we have calculated the activation barriers for the BV rearrangement of the six-membered Criegee intermediate and its hydroperoxy version (Scheme 9).<sup>84</sup>

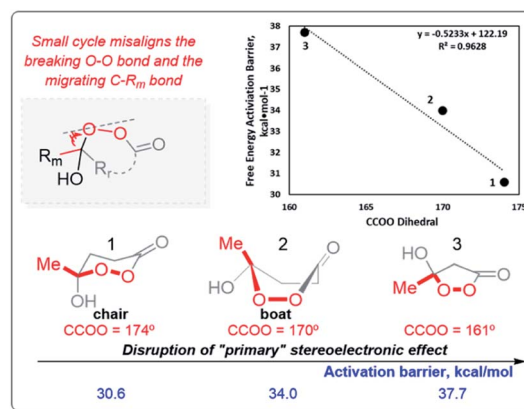
Both of the barriers were found to be considerably lower than the barriers for five-membered analogues illustrating that the C–R<sub>m</sub>/O–O bond alignment (the primary BV stereoelectronic effect) is a powerful protecting force for the Criegee intermediate.<sup>21</sup> Increasing the cycle size removes this protecting force and makes these compounds much more vulnerable to the BV rearrangement. This vulnerability explains why preparation of the six-membered CIs has been so challenging.

Comparison of computed barriers for the chair conformations of the six-membered CI and its hydroperoxy version also illustrates that, in this case, the protective power of inverse  $\alpha$ -effect is smaller than the effect of a five-membered ring. In particular, the free energy barrier for Me group migration is increased by only 3 kcal mol<sup>-1</sup> for the chair conformations of the OOH–CI relative to its OH-counterpart (Scheme 9). For the Et group migration, the difference is even smaller, ~1 kcal mol<sup>-1</sup>. Interestingly, even with this extra protection, the BV barrier for the Et/OOH derivative is still lower than it is for the Me/OH derivative.

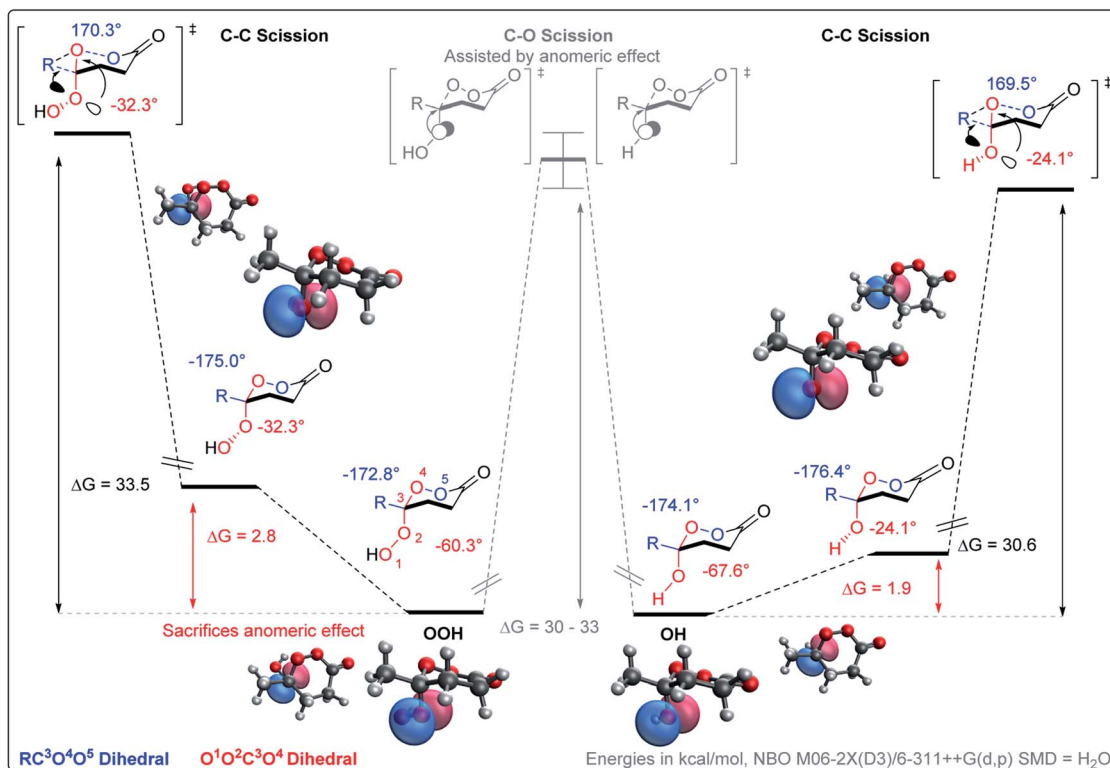
### Additional complexity – the chair/boat equilibrium.

However, the conformational profile of the six-membered peroxy lactones has an additional peculiarity that our computations have, for the first time, identified as a supplementary source of kinetic protection for the six-membered CIs. As mentioned

earlier, the preferred conformation of these species is the boat, but the BV reaction proceeds through a chair TS. Although the chair TS is lower in the absolute free energy than the boat TS (~1.6 and 0.1 kcal mol<sup>-1</sup> for the OH and OOH derivatives, respectively), the need to adopt the reactive chair conformation is an additional Curtin–Hammett penalty that can be evaluated as ~1.8 and 2.4 kcal mol<sup>-1</sup> for the OH and OOH derivatives, respectively (Scheme 10). Such effect is not negligible since it should lead to >10-fold deceleration of the 1,2-methyl shift for the OH derivative. Furthermore, the presence of two energetically close but geometrically different transition states for the 1,2-shift should have implications for the design of stereoselective Baeyer–Villiger rearrangements of the six-membered peroxides (Scheme 11).



Scheme 12 The activation barriers for the BV rearrangement of the six- and five-membered Criegee intermediates.



Scheme 13 Anomeric effect as “the fourth stereoelectronic effect” in the BV rearrangement. R is the migrating substituent. The scheme illustrates the cost of giving up the anomericly stabilized OOH conformation in order to adopt a reactive conformation that satisfies the BV “primary stereoelectronic effect”. The energies of the OH and OOH CIs are taken the same for illustration purposes.

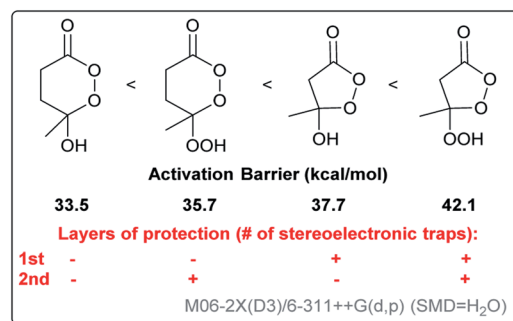
**Origin of the boat/chair effect on the BV barrier – interfering with the “primary stereoelectronic effect”.** The  $R_m\text{COO}$  dihedral in hydroperoxides with  $R = \text{Me}$  chair is  $-174.1$  and boat is  $171.4$  (similar to peroxy lactones in Scheme 12). Although, this is not a large change but it suggests one more way to weaken the primary stereoelectronic effect in BV reaction – to start from a boat, rather than a chair conformation.

However, this is not the end of this stereoelectronic story because a more detailed computational analysis of the reaction path reveals one more “hidden” stereoelectronic factor related to the second BV stereoelectronic effect. We will discuss this effect in the following section.

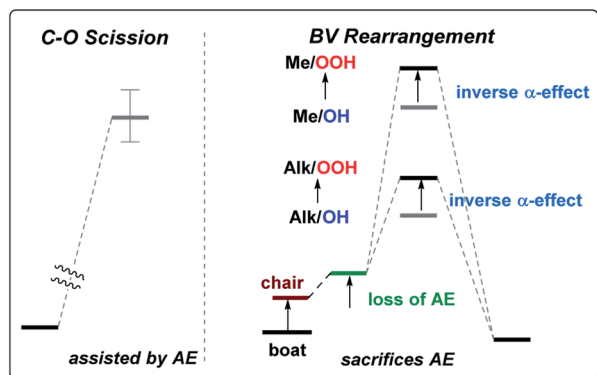
**Competition with the C–O scission – the two roles of the anomeric effect in the Curtin–Hammett scenario.** In the BV reaction, the lone pair of oxygen has to give up (sacrifice) its stabilizing anomeric interaction with the  $\sigma_{\text{CO}}^*$  orbital in order to start assisting with the migration of the  $R_m$  (*i.e.*, participate in the “secondary stereoelectronic effect of BV reaction”). This is an example of “orthogonal” stereoelectronic effect on reactivity, or “unproductive ground state stabilization”.<sup>85</sup> Because loss of the anomeric effect is an additional penalty that every BV reaction should go through, anomeric effect is the additional stereoelectronic force that protects the Criegee intermediates from following the BV path.

In order to evaluate the extent of anomeric stabilization that our systems have to lose when the lone pair of the exocyclic oxygen atoms is aligned with the C–R bond instead of the C–

O(OR) bond, we have optimized these molecules with the OOCR dihedral constrained to their value in the respective BV transition states. The energy difference between this conformation and the most stable conformation of the reactant evaluates the degree of anomeric stabilization that the molecule sacrifices in order to satisfy the “secondary stereoelectronic effect in the BV”. Scheme 13 summarizes the energetic consequences of anomeric effect for the competition between BV rearrangement and simple C–O scission that leads to the opening of the peroxide ring. C–O scission, the observed reaction path, wouldn’t need to sacrifice the AE effect (the  $n_{\text{O}} \rightarrow \sigma_{\text{CO(O)}}^*$  interaction can continue to get stronger in the process of  $\text{C}\cdots\text{O}(\text{O})$  bond scission).<sup>86–88</sup> On



Scheme 14 The free energy activation barriers for the non-catalyzed BV rearrangement of the six- and five-membered Criegee intermediates depending on the layers of protection.



Scheme 15 The three stereoelectronic factors in the BV rearrangement working together to protect the six-membered Criegee intermediate (AE = anomeric effect).

the other hand, the OH (or OOH) group has to give up the AE stabilization in order to have an appropriate conformation for participation in the “secondary stereoelectronic effect” in BV rearrangement. In the ground state, the lone pair is aligned with the endocyclic C–O bond. However, the lone pair of the adjacent oxygen realigns with the breaking C–C bond to the migrating group in the BV TS when there is a significant positive charge develops at the migrating group. Development of positive charge at the methyl group is difficult, as illustrated by the instability of the methyl cation. Hence, the lone pair does not offer its assistance to the C–C scission and the C–O scission is observed instead.

## Conclusions

The protective power of inverse  $\alpha$ -effect weakens upon transition from a five-membered to a six-membered CI (from 4.4 to 2.2 kcal mol<sup>-1</sup> for the parent compounds) (Scheme 14). However, this power is still sufficient for preventing the Baeyer–Villiger rearrangement of  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactones with methyl-substituent in the C6-position. Such compounds were prepared selectively *via in situ* peroxidation/cyclization of  $\gamma$ -ketoesters with a BF<sub>3</sub>·Et<sub>2</sub>O/H<sub>2</sub>O<sub>2</sub> system.

A variety of  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactones with a methyl-group at the C6-position and a wide scope of substituents at the C5-position were isolated in moderate to good yields. Attempts to prepare  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactones with a primary alkyl or an aryl group at C6 led to Baeyer–Villiger products. Treatment of  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactone **2a** by Ph<sub>3</sub>P led to selective reduction of hydroperoxyl-group with the formation of  $\gamma$ -hydroxy- $\gamma$ -peroxylactone **3a**. Although the latter is quite unstable and transformed into a mixture of  $\gamma$ -ketoacid and, probably,  $\gamma$ -ketoperacid, we were able to isolate and characterize **3a**. This cyclic peroxide provides the first example of the Criegee intermediate constrained in a six-membered ring, where it is not protected by pronounced misalignment of the two breaking bonds (C–R<sub>m</sub> and O–O).

These surprising observations motivated us to explore these systems deeper and led to the discovery of two new

stereoelectronic effects important for the BV process – the chair/boat transition and a hidden penalty for the loss of anomeric effect along the reaction path. These effects can amplify the protective power of inverse  $\alpha$ -effect in the peroxy-derivatives and provide marginal stability to the OH-CIs to the extent where the C–O bond scission starts to be observed. Interestingly, this is a new reactivity direction for CIs under the neutral conditions.

We have also identified a hidden role that the anomeric effect plays in the fate of Criegee intermediate – the loss of the reactant anomeric  $n_{\text{O}} \rightarrow \sigma_{\text{C-O}}^*$  stabilization has to happen in order to activate the “second stereoelectronic effect” (*i.e.*, to realign the lone pair of the exocyclic oxygen with the breaking C–R bond). This sacrifice adds an additional level of kinetic protection for the peroxy CI.

In summary, this work further expanded the growing list of stereoelectronic effects in peroxide chemistry.<sup>89–91</sup> We have identified and compared contributions of four effects of potential importance for the BV rearrangement: (a) “primary and secondary stereoelectronic effects”, – two effects that stabilize the TS of the final 1,2-alkyl shift (or withhold this stabilization either in the presence of structural constraints or due to the inverse  $\alpha$ -effect) and (b) boat/chair conversion and exo-anomeric effect – the two effects that stabilize the reactant but have to be sacrificed in order to reach the TS (Scheme 15). By understanding the interplay of these stereoelectronic factors, a much deeper understanding of the possible CI transformations is possible including the newly found switch from 1,2-alkyl shift to C–O bond scission. The discovery of a simple method for synthesis of previously elusive  $\gamma$ -hydroperoxy- $\gamma$ -peroxylactones expands the list of possible synthetic routes to cyclic peroxides with promising spectrum of potential biological activity.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Synthesis and experimental studies of peroxides were supported by the Russian Science Foundation (Grant No. 18-73-00315). X-ray study of **2m** was carried out with financial support from Ministry of Science and Higher Education of the Russian Federation using the equipment of Center for molecular composition studies of INEOS RAS. Computational analysis at FSU was supported by the U.S. National Science Foundation (CHE-1800329, I. V. A.).

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