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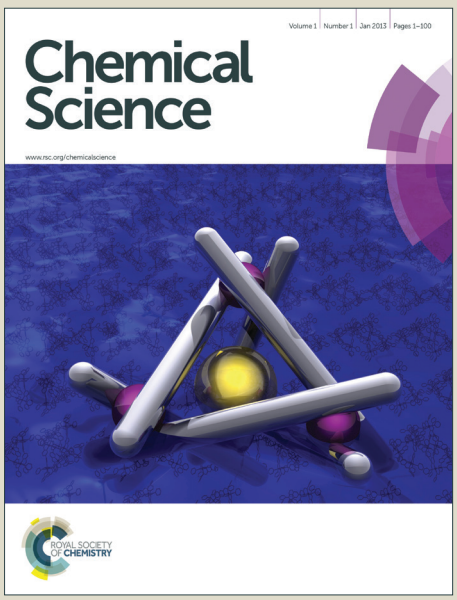

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Mechanistic insights into the malonoyl peroxide *syn*-dihydroxylation of alkenes

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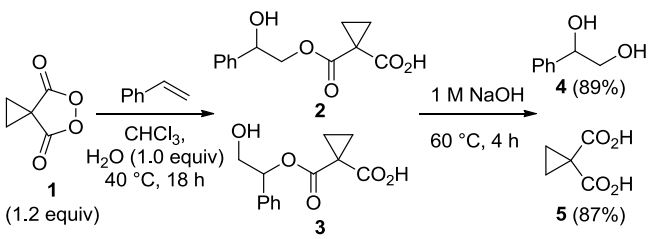
A detailed mechanistic understanding of the malonoyl peroxide mediated dihydroxylation of alkenes is presented. The reaction is first order in both alkene and peroxide with stoichiometric water playing a dual role. An ionic mechanism is proposed and supported by the use of ^{18}O isotopically labelled peroxide, a radical clock probe and DFT calculations. Hammett analysis suggests the reaction proceeds *via* a discrete carbocation intermediate which is consistent with the stereochemical outcome of the transformation. A subsequent Woodward-type 1,3-dioxolan-2-yl cation has been trapped *in situ* and the mechanism of hydrolysis defined by isotopic labelling studies. Stable reaction intermediates have been isolated and characterised by X-ray crystallographic analysis and minor competing reaction pathways identified.

Introduction

The Sharpless Asymmetric Dihydroxylation (SAD) represents a key landmark in the history of asymmetric catalysis providing a practical, accessible, and useful method to perform a fundamental transformation. More than 20 years after its introduction SAD remains the gold-standard in alkene functionalisation due its outstanding substrate scope, high levels of asymmetric induction, consistently high yields, and simplicity.[1] The toxicity, cost and limited abundance of osmium, which is required for this reaction, has provided the incentive to develop improved procedures. In recent years the chemical community has responded to this need with reports describing both metal-catalysed[2] and metal-free reactions.[3]

A key focus within the emerging field of metal-free procedures is the delivery of sustainable processes. The realisation of alternatives to precious metal catalysts is a primary objective where the advantages of cost and availability would have significant impact on industrial applications. To date, a general metal-free catalytic asymmetric alkene *syn*-dihydroxylation remains an elusive and important target. A powerful and inventive body of work has recently been directed towards achieving this ultimate goal.[3] For example, significant advances have been made using either peroxides[4] or hypervalent iodine[5] species to perform the transformation. Efforts using selenium[6] and sulfur[7] reagents have also been reported but these remain significantly less developed.

A simple and effective method for the *syn*-dihydroxylation of alkenes using malonoyl peroxides is outlined in Scheme 1.[4b] Reaction of peroxide **1** (1.2 equiv) with styrene in the presence of water (1.0 equiv) leads to the esters **2** and **3**. Basic hydrolysis of the crude reaction mixture provides diol **4** (89%) and diacid **5** (87%) which can be recycled (Scheme 1). The high stereoselectivity, functional group tolerance, and mild reaction conditions together with the easy preparation of **1** render this an outstanding reaction with significant potential for further exploitation.

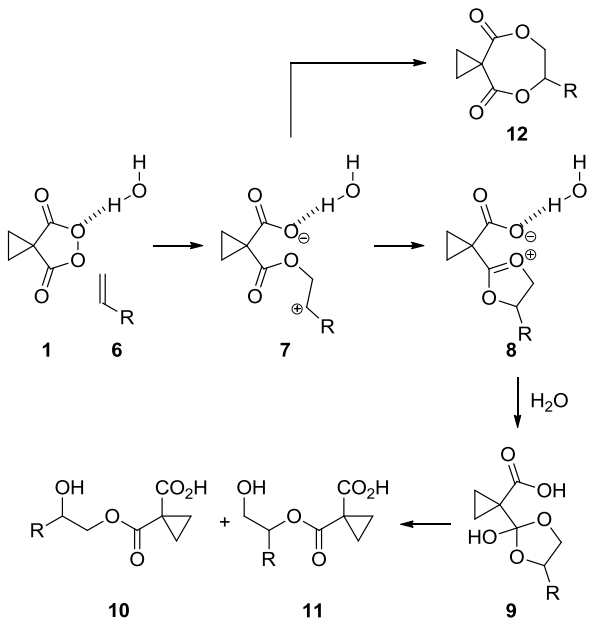


Scheme 1. Dihydroxylation of styrene with malonoyl peroxide **1**.

For a catalytic asymmetric variant of this transformation to be delivered, a thorough mechanistic understanding of the reaction will be required.[8] Without this, advancement will remain a random screening exercise with little chance of success. Within this manuscript we define the mechanistic pathway for this malonoyl peroxide mediated alkene *syn*-dihydroxylation that meets the central challenge in the evolution of this new synthetic procedure and define key intermediates which could be exploited in the invention of new bond construction procedures.

The literature mechanism for the transformation is outlined in Scheme 2 although little evidence has been presented to

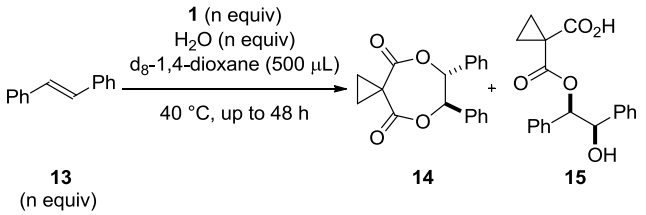
support this pathway.[4] Reaction of alkene **6** and peroxide **1** leads to **7** which undergoes ring closure, forming dioxonium species **8**. Hydrolysis with the molecule of water necessary to bring about reaction gives esters **10** and **11**. In addition, a small amount of the 7-membered ring intermediate **12** forms, which is a result of direct intramolecular cyclisation of the zwitterionic species **7**. Water plays a pivotal role within this transformation, activating peroxide **1**, stabilising a developing negative charge on oxygen (*i.e.* **7**), and hydrolysing intermediate **8** to give the observed isomeric products **10** and **11**.



Scheme 2. Proposed mechanistic sequence for the dihydroxylation process.

Results and Discussion

Investigations to unravel the mechanistic course of this transformation began by determining the kinetic orders of each reaction component. Homogeneous solutions of *trans*-stilbene **13**, peroxide **1**, and water in d_8-1,4-dioxane were monitored over time by ^{1}H NMR spectroscopy (Scheme 3). The reaction proceeded with clean conversion of starting materials to dioxygenated products **14** and **15** (Figure 1). Resubjection of **14** and **15** independently to the reaction conditions showed both of these products to be stable with no decomposition observed.



Scheme 3. Homogeneous reaction conditions used to obtain kinetic data.

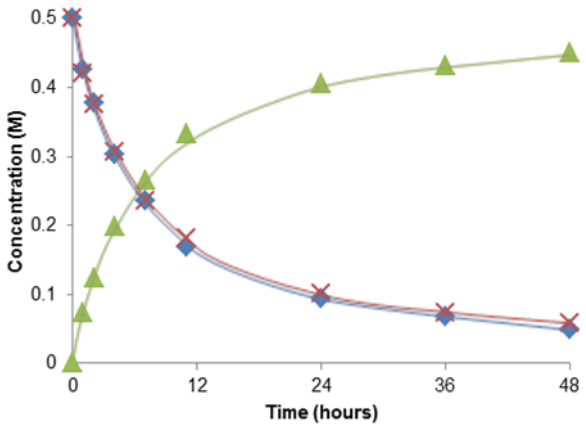
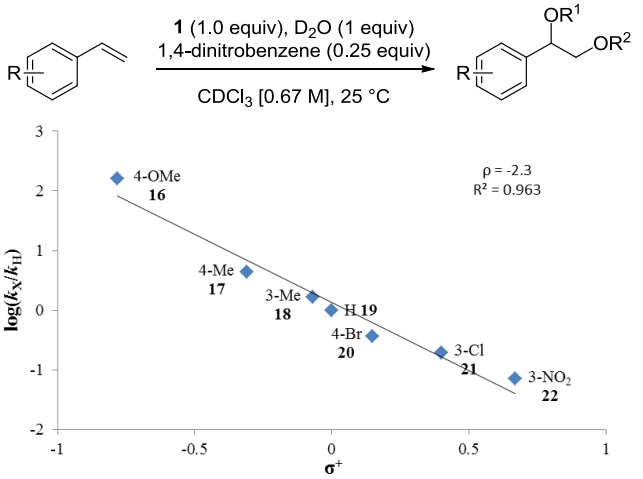


Figure 1. Reaction profile of the malonoyl peroxide **1** (X, 0.5 M) mediated dihydroxylation of *trans*-stilbene **13** (♦, 0.5 M) in the presence of one equivalent of water (0.5 M) leading to products **14** and **15** (▲).

The dihydroxylation reaction was found to obey second-order kinetics with a first-order dependence in both alkene and peroxide ($k = 8.89\times10^{-5}$ $M^{-1}s^{-1}$, 40 °C, 1,4-dioxane). Water has a small catalytic effect through hydrogen bonding,[4c] although the effect was negligible such that the reaction is approximately zero-order in water (see the Supplementary Information for full details).

To gather evidence for the involvement of a discrete carbocation intermediate (*e.g.* **7**), the reaction was subjected to Hammett analysis (Scheme 4). A series of substituted styrene derivatives **16**–**22** were treated with one equivalent of peroxide **1** under the reaction conditions outlined in Scheme 4 (see the Supplementary Information for full details). The rate of peroxide consumption was monitored relative to an internal standard by ^{1}H NMR spectroscopy and the initial rates used to construct the Hammett plot shown based on literature σ^+ values.[9]



Scheme 4. Hammett plot for the reaction of styrenes **16**–**22** with peroxide **1**.

The Hammett plot showed an excellent linear relationship indicating that the same mechanism is in operation for both electron-donating and electron-withdrawing substituents. The gradient of the line, ρ, gave a moderate negative value of -2.3 indicating a considerable build-up of positive charge during the transition state, consistent with a benzylic carbocation (*e.g.* **7**). As expected, reactions of electron-rich styrene derivatives (*e.g.* **16**) proceeded at a significantly faster rate than that of electron-deficient styrene derivatives (*e.g.* **22**). The best correlation was achieved using σ^+ values. σ values produced a characteristic bent plot, with electron-rich styrenes (4-OMe **16** and 4-Me **17**) deviating from the trend (see the Supplementary Information for full details). This suggests that through-conjugation effects are important, consistent with a discrete benzylic carbocation intermediate (*e.g.* **7**) in a stepwise mechanism.

How malonoyl peroxides react with alkenes has not been established and this represented a fundamental challenge within this work. Numerous possibilities exist for this reaction to arrive at a carbocation intermediate including an ionic interaction, a radical process or a single electron transfer (SET). Literature precedent suggested that the related phthaloyl peroxides react with alkenes through an ionic mechanism.[10] It has also been shown that phthaloyl peroxide can undergo homolytic cleavage[11] and a recent report has shown it to be effective in the oxidation of arenes *via* a radical mechanism.[12] To understand this pivotal interaction between the alkene and the peroxide a number of reactions have been performed.

Reaction of *trans*-stilbene **13** with peroxide **1** (H_2O 1 equiv, $CHCl_3$, 40 °C, 0.6 M) was performed in both the presence and absence of light. No difference in reaction rate, yield or diastereoselectivity was observed, implying that a light-induced radical process was not operating.

The opening of cyclopropyl rings is an established method for the detection of radical intermediates in synthetic chemistry.[13] The Newcomb clock was elegantly designed to distinguish between ionic and radical mechanistic pathways.[14] We postulated that evidence for (or against) a radical or ionic mechanism could be gained by using alkene **23** as a substrate. If the mechanism proceeded *via* a radical intermediate (*e.g.* **24a**) cleavage of the C_2—C_3 bond would be expected, forming a benzylic radical (Figure 2). If the reaction proceeded *via* a carbocation intermediate (*e.g.* **24b**) cleavage of the C_1—C_3 bond would be anticipated, forming an oxonium ion.

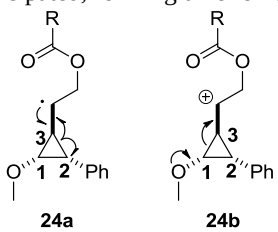
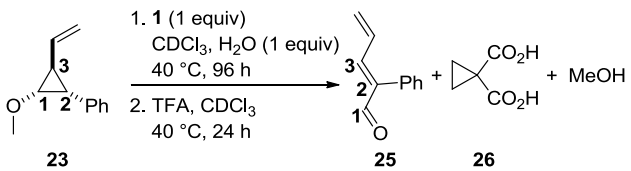


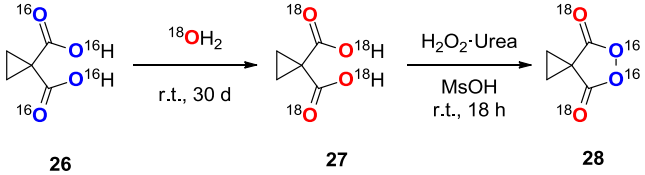
Figure 2. Plausible ring opening of radical and cationic Newcomb clock intermediates.

Alkene **23** was prepared from *cis*-β-methoxystyrene, as previously reported, as a single diastereomer.[14] Reaction of **23** with 1 equivalent of peroxide **1** (Scheme 5) led to complete consumption of both starting materials to give a complex mixture of products as observed by ^{1}H NMR spectroscopy. Addition of TFA to the crude reaction mixture led to convergence of these intermediates to dienal **25** (>90%), diacid **26** and methanol as the major reaction products (see the Supplementary Information for full details). The connectivity of dienal **25** is consistent with cleavage of the C_1—C_3 bond in **23** and provides strong evidence for an ionic mechanism.



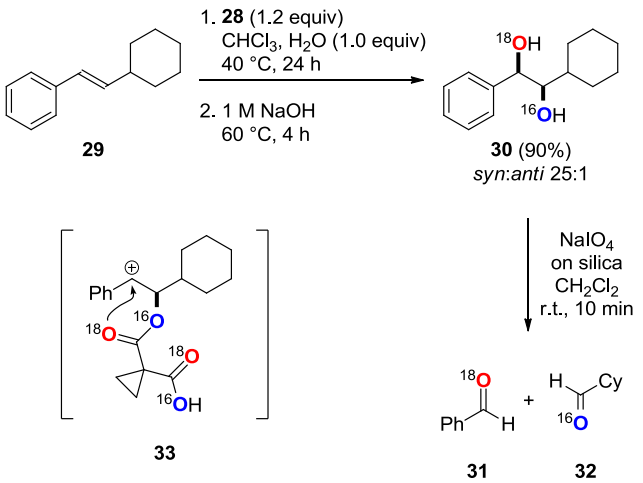
Scheme 5. Reaction of Newcomb clock alkene **23** with **1**.

Further evidence for an ionic mechanism came from the preparation and reaction of the differentially labelled peroxide **28**. Stirring the carboxylic acid **26** in ^{18}O-labeled water ($^{18}OH_2$) at room temperature for 30 days provided the labelled derivative **27**. Mass spectrometric analysis (ESI) showed incorporation of the ^{18}O label into **27** to be greater than 75%. This ^{18}O-enriched carboxylic acid **27** was treated with urea hydrogen peroxide complex[15] in the presence of methane sulfonic acid to give the differentially labelled peroxide **28**.[16] It was not possible to ascertain the precise location of the label(s) or identify the number incorporated into the product **28** through mass spectrometry, however, the results described below for the reaction of **28** with an alkene are consistent with the structure shown.



Scheme 6. Preparation of differentially labelled peroxide **28**.

Reaction of the peroxide **28** with unsymmetrical alkene **29** followed by hydrolysis gave the expected diol **30** (90%, *syn*:*anti* 25:1). Mass spectrometric analysis of diol **30** showed incorporation of one ^{18}O-labeled oxygen atom, with the fragmentation pattern suggesting this was located in the benzylic position. Oxidative cleavage of diol **30** under anhydrous reaction conditions[17] gave the corresponding aldehydes **31** and **32** where the ^{18}O label was incorporated exclusively into benzaldehyde **31** and not cyclohexanecarboxaldehyde **32** by GC-MS analysis (Scheme 7). These powerful results are consistent with an ionic interaction between the peroxide **28** and the alkene **29** forming the most stable (benzylic) carbocation intermediate **33**. Ring-closing of the adjacent ^{18}O-labeled carbonyl oxygen onto this carbocation followed by hydrolysis then gives the observed product.



Scheme 7. Dihydroxylation with differentially labelled peroxide **28**.

This result is significant and reveals a number of properties of the peroxide **28**. Under the reaction conditions no scrambling of the label is observed. This suggests the oxygen—oxygen bond in **28** does not readily undergo homolytic fission to give the di-radical **34** and scramble the label to give **35** and **36** (Figure 3). Use of a mixture of **28**, **35** and **36** in the dihydroxylation of **29** would lead to a non-regioselective incorporation of the ^{18}O label into the alkene substrate which is not observed.

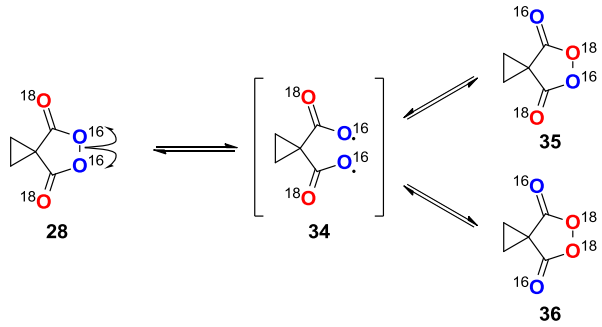


Figure 3. Potential scrambling of label through homolytic fission of peroxide bond in **28**.

To investigate the interaction between alkene and peroxide further we used DFT calculations. A number of possibilities were examined including a concerted reaction, an ionic pathway, a radical process and single electron transfer (SET).

For an ionic process two discrete transition states **TS1** and **TS2** were found which differ in the relative orientation of peroxide and alkene (Figure 4). Following the intrinsic reaction coordinate from **TS1** (ΔG = 29.5 kcal mol^{-1}) leads to the dioxonium species **37**, a structure consistent with the proposed mechanistic course of the reaction. It was possible that **37** could arise by a concerted process with simultaneous O—O bond cleavage and C—O bond formation, but on close inspection of the reaction coordinate a high-energy intermediate **38** (19 kcal mol^{-1}) was clearly present suggesting a concerted mechanism was not operating. **TS2** (ΔG = 30.6 kcal mol^{-1}) was higher in energy than **TS1**, but equally accessible. The intrinsic reaction coordinate from **TS2** leads to an open chain zwitterionic species **39** which is 21.8 kcal mol^{-1} higher in energy than **37**. In the reaction of *trans*-stilbene **13** we expect each of these transition states, which arise from different approaches of the peroxide and alkene, to be equally likely but it should be possible to influence these barriers based upon the structure of starting alkene.

Additional support for an ionic interaction came from inspection of the calculated LUMO for peroxide **1** (B3LYP/6-31+G**) showing the σ* orbital for the oxygen—oxygen bond is readily accessible to nucleophilic attack (Figure 5).

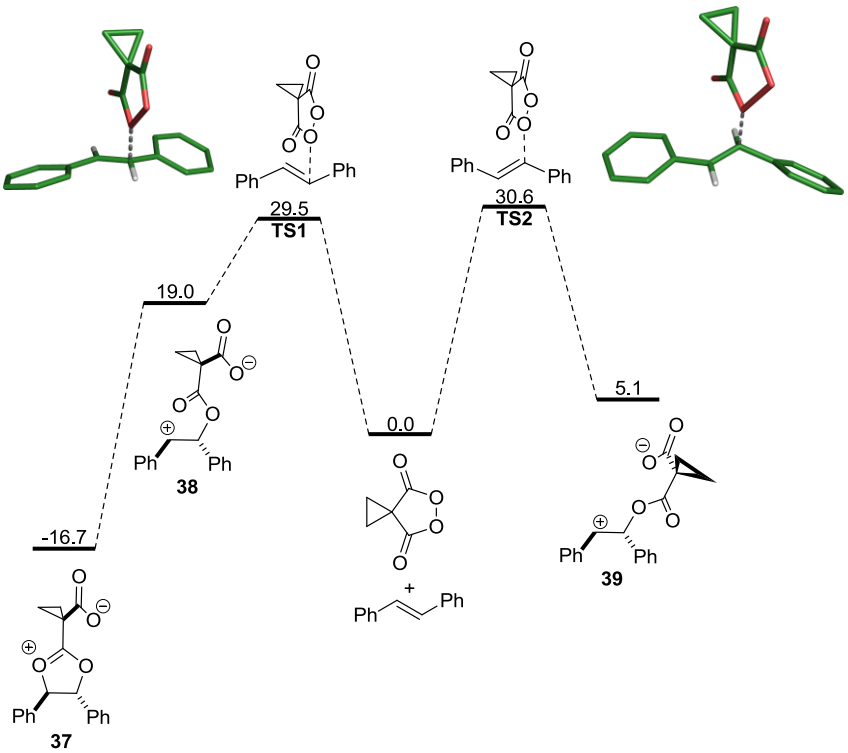


Figure 4. Transition states for the reaction of *trans*-stilbene **13** with peroxide **1** (energies in kcal mol^{-1}).

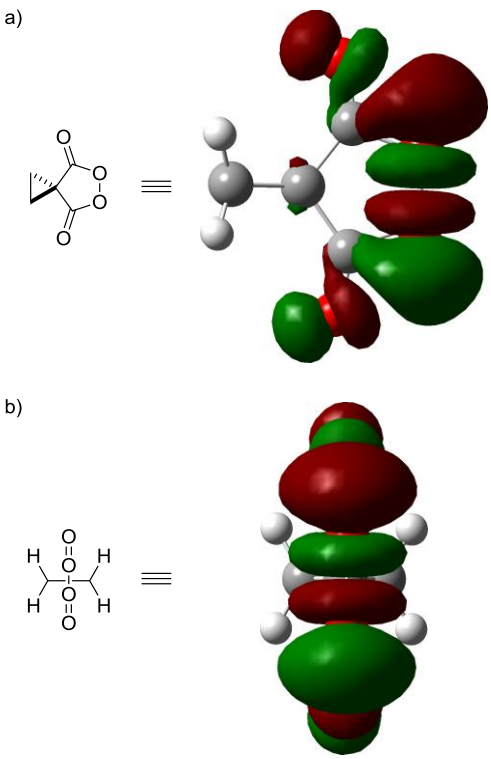
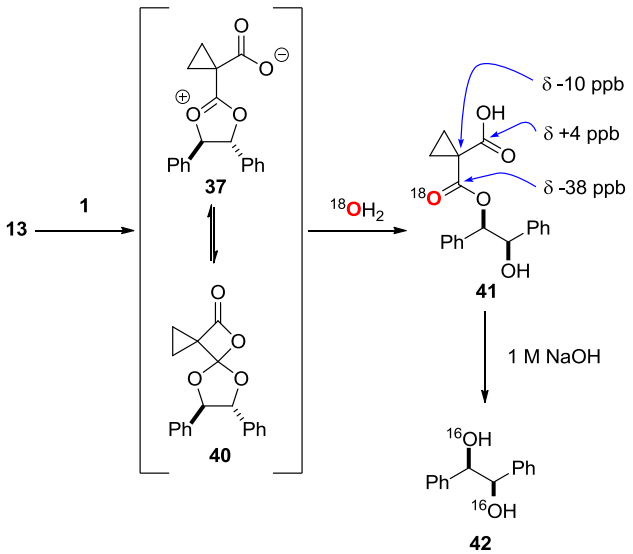


Figure 5. Calculated LUMO for peroxide **1** a) Side view. b) Front view.

Having found a potential reaction pathway for an ionic mechanism focus turned to evaluating a radical pathway. A transition state for homolytic cleavage of the oxygen—oxygen bond into a diradical species was found (28.9 kcal mol^{-1}). However, no interactions between the diradical and *trans*-stilbene **13** could be found such that DFT calculations provided no evidence to support a radical pathway (see the Supplementary Information for full details) in contrast to the findings of Houk on the reaction between phthaloyl peroxide and arenes.[12] A SET pathway was also investigated computationally. The combined energy of the radical anion of peroxide **1** and radical cation of *trans*-stilbene **13** was found to be 98.4 kcal mol^{-1}, which is significantly higher than **TS1** or **TS2**. These findings are consistent with those reported by Houk[12] and suggest that a SET process would be unlikely to occur between **1** and **13**. In combination these computational results provide strong evidence for an ionic interaction between the alkene substrate and peroxide reagent.

Having gathered evidence the reaction was occurring in a stepwise manner *via* an ionic interaction leading to the carbocation **7**, our attention focused on the second proposed intermediate dioxonium **8**. The results described in Scheme 7 using the labelled peroxide **28** are consistent with such a dioxonium intermediate. In the reaction of *trans*-stilbene **13** this species could exist as the zwitterion **37**, its protonated derivative, or the spirocycle[4d,10b] **40** (or a mixture). Conducting the reaction of peroxide **1** and *trans*-stilbene **13** in the presence of one equivalent of $^{18}OH_2$, ($CHCl_3$, 40 °C) provided the expected *syn*-product **41** (79%) which showed incorporation of a single oxygen label into the product by mass spectrometry. ^{13}C NMR spectroscopy of the product showed a 38 ppb upfield movement in the chemical shift of the ester carbonyl carbon (Scheme 8). The chemical shift of the carboxylic acid carbonyl carbon changed by +4 ppb when compared to the product

derived from $^{16}OH_2$. In addition, the chemical shift of the quaternary carbon of the cyclopropyl ring moved by -10 ppb when compared to the unlabelled variant. Overall this data is consistent with incorporation of the ^{18}O label into the ester carbonyl carbon of **41** and not the carboxylic acid carbon.[18] Hydrolysis of intermediate **41** under basic reaction conditions provided the expected diol **42** (93%, *syn:anti* 33:1) with no ^{18}O label observed in the newly formed carbon—oxygen bonds. Consistent with these data is the direct nucleophilic addition of water to the dioxonium intermediate **37** and not the ring opening of the α-lactone **40**.



Scheme 8. Reaction of *trans*-stilbene **13** in the presence of $^{18}OH_2$.

Although this result is consistent with the reaction of water with intermediate **37** it does not provide information on **40**. This was investigated further by examination of **37** and **40** through DFT calculations (B3LYP/6-31+G**) using a chloroform PCM. This showed that spirocycle **40** was 5.8 kcal mol^{-1} more stable than zwitterion **37** (Figure 6), suggesting it could exist as a reaction intermediate. It is possible **37** and **40** are in rapid equilibrium in the reaction, with **37** being more reactive to water.

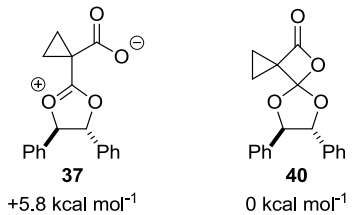
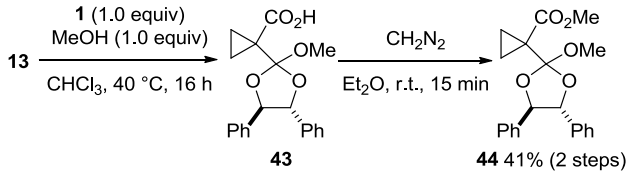


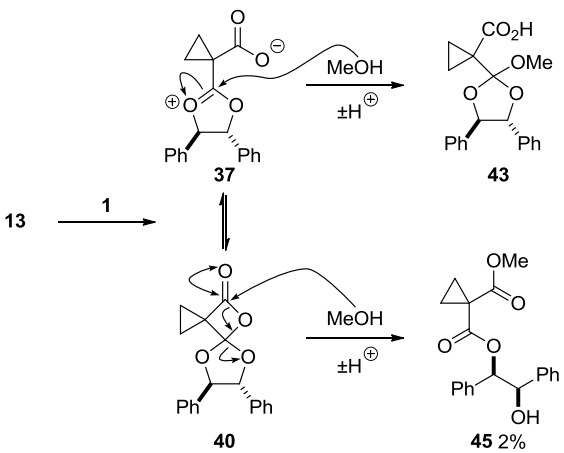
Figure 6. Low energy structures for potential intermediates **37** and **38**.

Further evidence for the existence of, and direct nucleophilic attack on the dioxonium species **37** came from a trapping experiment. The peroxide **1** reacts with alcoholic solvents,[4c] but this is at a slower rate than reaction with an alkene. Therefore treatment of *trans*-stilbene **13** with peroxide **1** in the presence of anhydrous methanol (1 equiv) provided the ortho-ester **43** (Scheme 9). It was not possible to purify **43**, which was unstable to silica gel chromatography. However, NMR spectroscopy on the crude reaction mixture was consistent with the structure shown (see the Supplementary Information for full details).[19] Treatment of an ether solution of crude **43** with diazomethane gave the corresponding methyl ester **44** in 41% isolated yield for the two steps. This proved to be a stable compound and could be purified by silica chromatography. These results show direct nucleophilic attack of methanol on the dioxonium **37**, consistent with the observations with water.

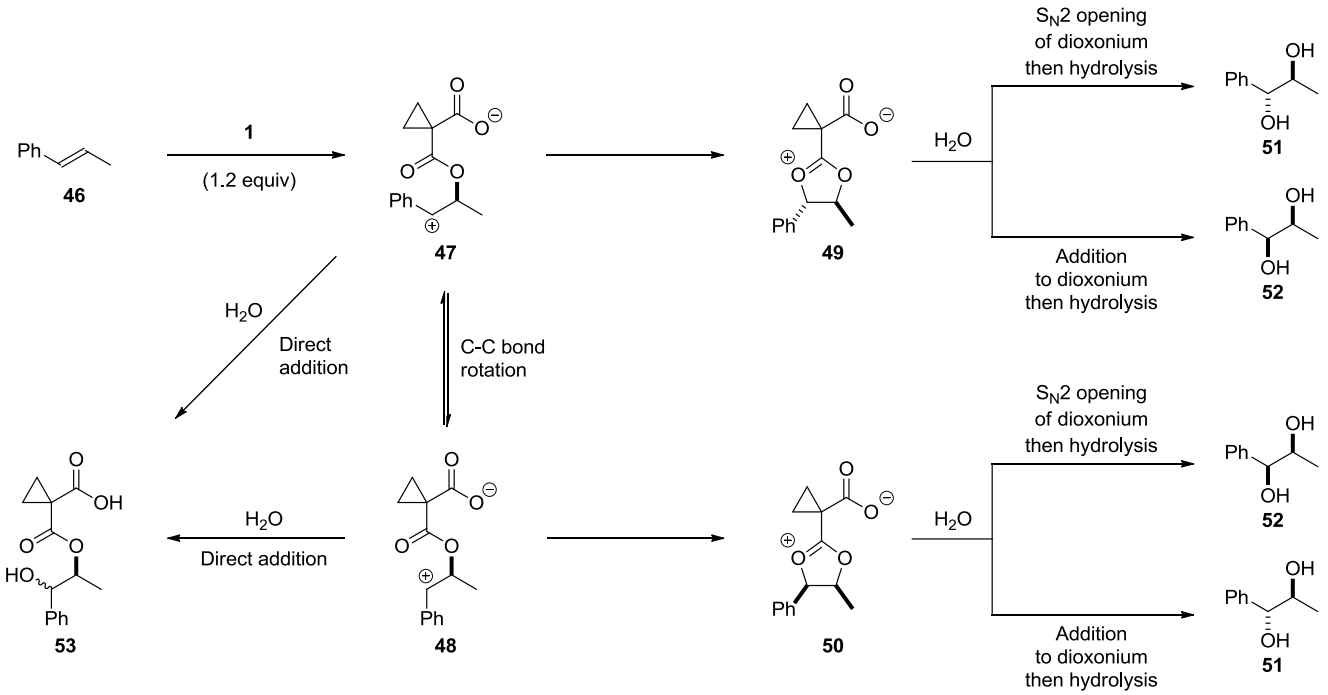


Scheme 9. Reaction of *trans*-stilbene **13** and peroxide **1** in the presence of anhydrous methanol.

Significantly, a small amount of methyl ester **45** (1:25 **45**:**43**) was observed in the ^1H NMR spectrum of the crude reaction mixture before treatment with diazomethane, and this was confirmed by independent synthesis of **45**. Methyl ester **45** presumably arises from nucleophilic attack by methanol on the β-lactone **40** (Scheme 10). Although only small quantities of **45** were formed, its presence provides strong experimental evidence for the spirocyclic lactone **40** proposed by the DFT calculations.



Scheme 10. Reaction of *trans*-stilbene **13** and peroxide **1** in the presence of anhydrous methanol.



Scheme 11. Potential mechanistic pathways for the *syn*- and *anti*- dioxygenation of 1,2-disubstituted alkenes.

In the dihydroxylation of 1,2-disubstituted alkenes (such as **46**) with malonoyl peroxides, two diastereomeric products arise; the *syn*- and *anti*- isomers. The dioxygenation is not stereospecific which provides further support the reaction proceeds in a step-wise manner *via* a carbocation intermediate (*e.g.* **47**). Three principal pathways can be envisaged which lead to a compromise in the stereoselectivity (Scheme 11). (i) The S_N2 ring opening of a dioxonium intermediate with water (*e.g.* **49**). (ii) Rotation about a C—C σ bond (*e.g.* **47→48**) followed by formation of a dioxonium (*e.g.* **50**) and hydrolysis. (iii) The direct attack of water on the carbocation intermediate (*e.g.* **47** or **48**). The absence of any detectable ^{18}O label in the diol product **42** from the dihydroxylation of stilbene (93% yield, *syn*:*anti* 33:1, Scheme 8) suggests that S_N2 ring opening of **37** on either of the benzylic carbons is not a significant mechanistic pathway for the transformation, however, the small amount of *anti*-product obtained in this reaction (93%, *syn*:*anti* 33:1) makes this challenging to determine unequivocally.

In further pursuit of understanding this loss of stereoselectivity we examined β-methyl styrene **46** as a substrate. Reaction of β-methyl styrene **46** with peroxide **1** (1.2 equiv) in the presence of $^{18}OH_2$ (1 equiv) led to the *syn*- and *anti*-diols **52** and **51** (*syn*:*anti* 16:1, 92%) after hydrolysis (Figure 7). These isomers were separable by HPLC providing authentic samples of **52** and **51**. Interestingly, the ^{18}O content of the *syn*-diol **52** was 0% whereas the ^{18}O content of the minor *anti*-diol **51** was 10%. This suggests that the rate of hydrolysis of dioxonium intermediates **49** and **50** is significantly quicker than direct S_N2 ring opening. In addition, these results suggest the loss in stereoselectivity mainly arises from the C—C bond rotation that forms **48** from **47** followed by dioxonium formation and hydrolysis rather than direct addition of water to **47** or **48** to give **53**. Closer inspection of the fragmentation pattern in the mass spectrum shows the ^{18}O label within the *anti*-isomer **51** is exclusively at the benzylic carbon consistent with S_N2 ring opening of **49** at the stabilised centre.

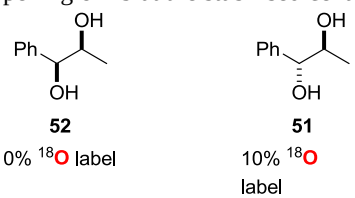


Figure 7. Incorporation of ^{18}O into β-methyl styrene products.

Consistency with this rationale for loss in stereochemical integrity came from further interpretation of previous data (Figure 8).[4b] Stabilisation of the carbocation intermediate through reaction of *trans*-anethole leads to a decrease in the stereoselectivity observed (**54**, *syn*:*anti* 5.5:1) when compared to the reaction of β-methyl styrene (**52**, *syn*:*anti* 16:1). Increased steric requirements of the alkene substituents through reaction of *cis*-stilbene ($CHCl_3$, 40 °C) also resulted in a significant loss in stereoselectivity (**56**, *syn*:*anti* 3:1) consistent with formation of a discrete carbocation and subsequent C—C bond rotation. Finally, increasing the steric bulk between the substituents on a *trans*-alkene (**55**, *syn*:*anti* >50:1) or introduction of cyclic constraints on a *cis*-alkene (**57**, *syn*:*anti* >50:1) leads to excellent levels of stereoselectivity.

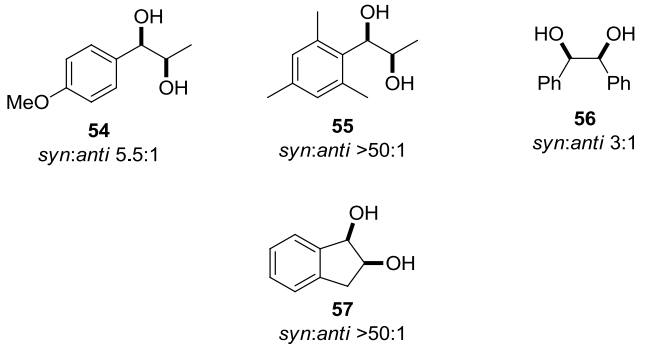


Figure 8. Dihydroxylation of alternative substrates.

Confirmation of the structures of intermediate products for the reaction of *trans*-stilbene **13** (prior to hydrolysis) came from single crystal X-ray analysis (Figure 9). Both the *syn*- and the *anti*-hydroxy esters **15** and **58** as well as the *syn*- and the *anti*-7 membered ring products **14** and **59** were prepared, isolated, and recrystallised as single diastereoisomers (see the Supplementary Information for full details). Interestingly, having an authentic sample of **59**, we were able to conclude that none of this compound was observed under our standard reaction conditions with *trans*-stilbene **13** as the substrate, implying the **7** membered ring intermediate **14** was formed stereospecifically within the detection limits of the ^{1}H NMR spectrometer.

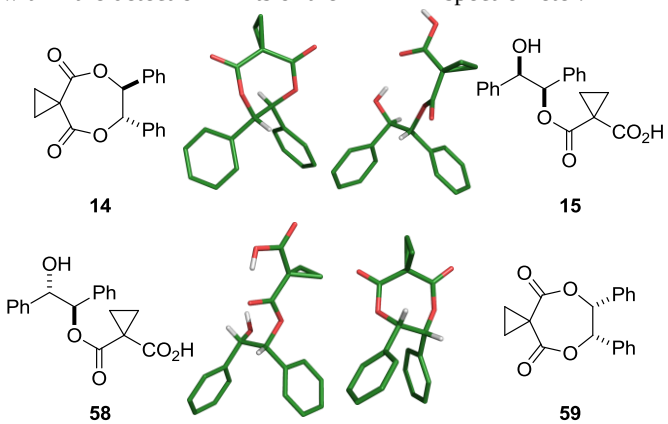
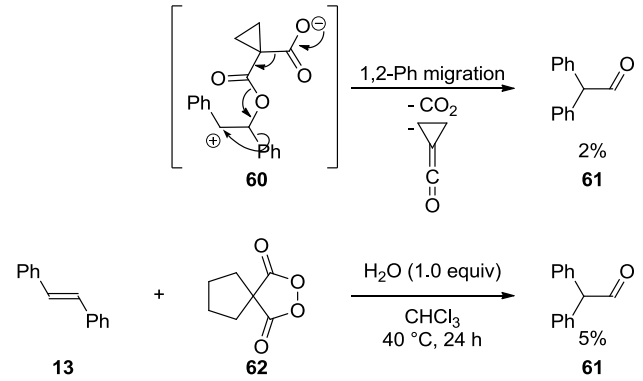


Figure 9. Single crystal X-ray structures of reaction products.

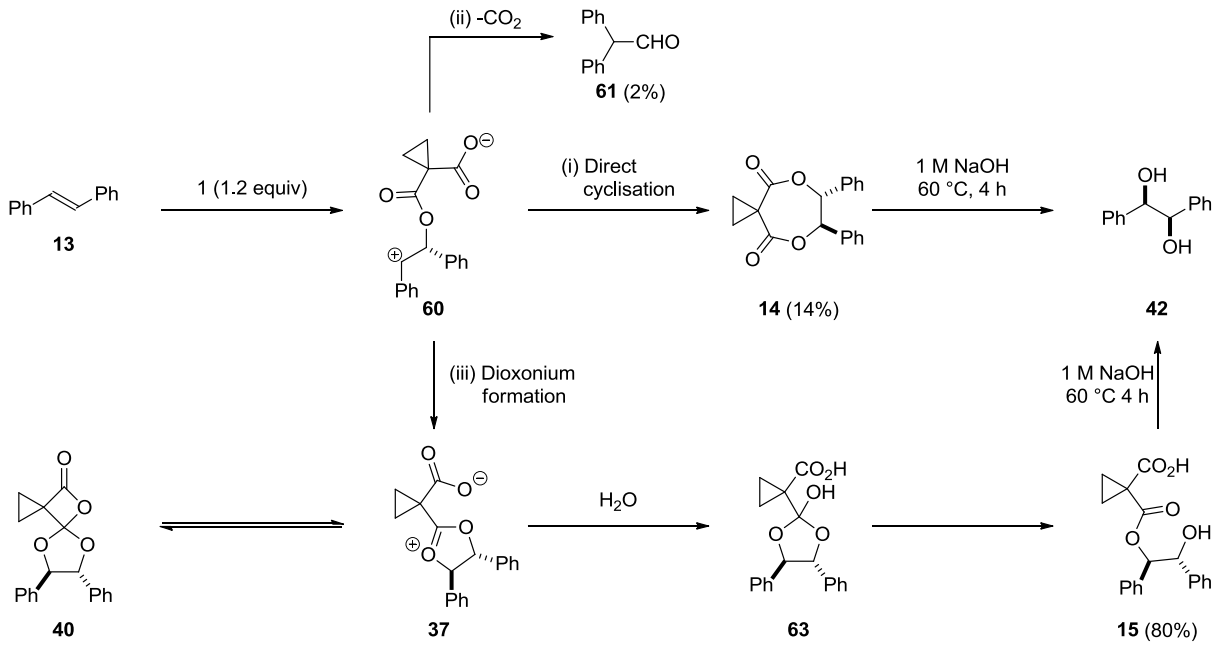
Up to this stage the products isolated accounted for 93% of the *trans*-stilbene **13** put into the reaction. Along with these products we were also able to isolate a small amount of the aldehyde **61** (2%) (Scheme 12). This semipinacol rearrangement product[20] is consistent with the formation of the zwitterionic intermediate **60**, decarboxylation and 1,2-phenyl migration to give the observed product **61**. Once again, this provides further strong evidence for the reaction proceeding in a step-wise manner through a carbocation intermediate. In previous work[4b] we had shown that the 5 membered ring peroxide **62** decarboxylated more readily than its cyclopropyl analogue **1**. This fact was borne out through careful examination of the crude reaction mixture from the reaction between *trans*-stilbene **13** and **62** where the rearranged product **61** was formed in a significantly higher yield of 5%.



Scheme 12. Formation of aldehyde product **61** *via* semipinacol rearrangement.

Conclusions

A detailed investigation on the mechanistic course of the reaction between peroxide **1** and alkenes has been presented. Consistent with our observations, an overall reaction sequence is presented in Scheme 13. Nucleophilic attack of the alkene on the peroxide **1** leads to the carbocation intermediate **60** which has three distinct fates: (i) direct cyclisation of the carboxylate onto the carbocation gives the 7 membered ring product **14** (14% yield for *trans*-stilbene), the structure of which was confirmed through X-ray crystallographic analysis. (ii) Loss of carbon dioxide and 1,2-migration of a phenyl group to give the aldehyde **61** (2% yield for *trans*-stilbene). (iii) Ring-closure to give dioxonium intermediate **37** (the major reaction pathway), which can form the more stable spirocycle **40**. Reaction of dioxonium species **37** with a molecule of water leads to the observed product **15** (80%). It proved possible to track the fate of the oxygen atoms from both the water molecule and the peroxide through isotopic labelling providing strong evidence for the reaction course. Hydrolysis of the crude reaction mixture containing both **14** and **15** leads to the *syn*-diol **42** in excellent yield and selectivity (93%, *syn*:*anti* 33:1). Stereoselectivity for the transformation is significantly influenced by the stability of the carbocation and the relative size of substituents on the starting alkene. The insight and knowledge provided by this fundamental study drives forward this important and highly relevant field of metal-free alkene functionalisation. Of particular note is identification of the key intermediate **37** which provides significant potential for additional novel bond construction processes through the addition of alternative nucleophiles.



Scheme 13. Proposed reaction sequence for the *syn*-dihydroxylation of alkenes with peroxide **1**.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterisation data, copies of NMR spectra for all compounds, detailed procedures for kinetics, DFT modelling and CIF files. See DOI: 10.1039/b000000x/

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