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anti-Dihydroxylation of olefins enabled by *in situ* generated peroxyacetic acid†

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Herein, we report a general and green protocol for the *anti*-dihydroxylation of unactivated alkenes. Combining H_2O_2 and acetic acid at 50 °C results in the formation of peroxyacetic acid, which enables the efficient synthesis of a wide range of *anti* 1,2-diols in moderate to good yields without the need for hazardous solvents or expensive transition metals as catalysts.

Since the establishment of the 12 principles of *Green Chemistry* over 25 years ago,[1] chemists have devoted considerable efforts and resources towards the development of more efficient, environmentally friendly, and sustainable chemical processes.[2,3] Good examples of this trend are the emergence of catalytic methods employing organometallic complexes based on earth-abundant metals (*e.g.*, Cu, Fe, Co, *etc.*);[4–6] the move towards the use of continuous-flow technologies to increase safety standards and improve process scalability;[7–9] and the conception of several metrics to quantify the efficiency or the environmental impact of a chemical process.[10–13]

The dihydroxylation of alkenes is a fundamental reaction in synthetic organic chemistry, which enables the preparation of either *syn* or *anti* 1,2-diols, key structural motifs found in a wide range of natural products and biologically active molecules.[14–17] While the *syn*-dihydroxylation of alkenes has been extensively studied, resulting in the development of a myriad of protocols,[18–20] the corresponding *anti*-dihydroxylation has received comparatively less attention.[21,22] This reaction typically occurs through epoxidation of the targeted alkene, which can be promoted by transition metal catalysis,[23–27] organocatalysis,[28–33] photocatalysis,[34,35] electrocatalysis[36,37] or biocatalysis,[38–40] followed by hydrolysis to generate the targeted *anti* 1,2-diols (Scheme 1A). Most of these processes require using (toxic) organic solvents, leading to increased waste generation,[1] or strong and non-sustainable oxidants to promote the key epoxidation step. Therefore, there is a need to develop greener protocols for the *anti*-dihydroxylation of alkenes based on the use of sustainable resources.

In 1926, Hilditch reported the *anti*-dihydroxylation of oleic and elaidic acids, as well as their corresponding methyl esters, using a combination of H_2O_2 and acetic acid to generate peroxyacetic acid, a strong oxidant capable of promoting the key epoxidation step (Scheme 1B).[41] While it took nine days at room temperature to produce the targeted products, the process could be significantly accelerated by increasing the reaction temperature. It was postulated that the existence of a dynamic equilibrium during the formation of the peroxy acid species was the main reason behind the slow reactivity at room temperature and the need for a high excess of H_2O_2.[42] Later, Swern reported that using catalytic amounts of sulfuric acid or replacing acetic acid by formic acid, shifts the equilibrium towards the formation of the key peroxy acid species and drives the reaction forward.[22,43] However, the use of these strong acids results in highly exothermic processes, thus increasing the overall risks associated with these reactions. To overcome this issue, researchers have established several strategies. For example: (a) the use of alternative acids (*e.g.*, *p*-toluenesulfonic acid) to form the key peroxy acid species catalytically,[44,45] (b) pre-forming the peroxy acid species *ex situ* by premixing the corresponding acid and H_2O_2,[46,47] or (c) the use of flow technology to increase the overall safety and scalability of the process.[48] Nevertheless, these approaches still rely on the use of strong and corrosive acids to form the reactive peroxy acid species, or convoluted approaches to avoid highly exothermic processes. Therefore, developing more sustainable and environmentally friendly processes for the *anti*-dihydroxylation of alkenes is highly desirable.

From a sustainability point of view, Hilditch's seminal contribution is almost ideal. It employs an eco-friendly and renewable solvent, such as acetic acid,[49,50] a relatively mild oxidant, such as H_2O_2,[51–53] and the sole by-product of the reaction is the formation of H_2O. More importantly, since the equilibrium constant for the formation of the peroxyacetic acid is low when mixing H_2O_2 and acetic acid at room temperature,[42,54] it does

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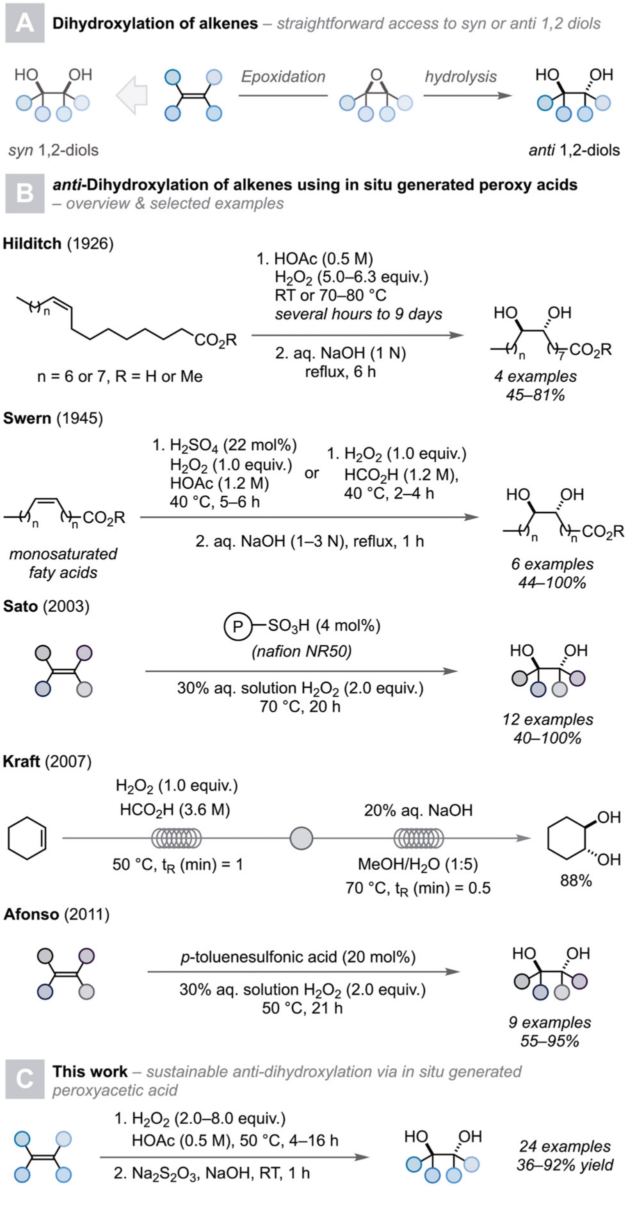


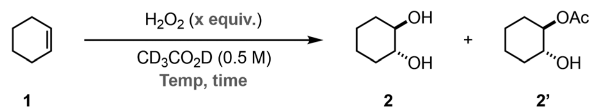
Scheme 1 *anti*-Dihydroxylation of alkenes using *in situ* generated peroxy acids – state of the art *vs.* this work.

not result in a highly exothermic reaction, as it is the case when using formic acid,[43,48] thus reducing the hazards associated with the transformation. However, the process was never fully optimised, it was sluggish, and the reaction scope was restricted to oleic and elaidic acid derivatives. Overall, these factors limited its synthetic applicability and uptake by the wider chemical community. Therefore, with the aim of developing a more sustainable process, we decided to revisit Hilditch's original work. Our goals were: (1) to optimise the reaction conditions, leading to efficient *in situ* formation of peroxyacetic acid and reduced reaction times, (2) to evaluate the reaction scope, and (3) to demonstrate the suitability of this sustainable strategy for the large-scale production of *anti* 1,2-diols. Herein, we report the results of our efforts: a general and environmentally friendly approach for the *anti*-dihydroxylation of alkenes, using acetic acid and a slight excess of H_2O_2, for the synthesis of a wide range of *anti* 1,2-diols (Scheme 1C).

We began the optimisation of the reaction conditions using cyclohexene **1a** as the model substrate (Table 1). The reactions were carried out in deuterated acetic acid, and the yield of the product(s) was calculated by ^{1}H NMR spectroscopy using trichloroethylene as the internal standard. Initially, a large excess of H_2O_2 (8.0 equiv.) was tested at 50 °C (Table 1, entry 1). To our delight, we observed complete consumption of **1** and formation of *trans*-cyclohexane-1,2-diol (**2**) and acetylated species **2′** in 40% and 25%, respectively, after 3 h. Decreasing the amount of H_2O_2 to 2.0 equiv. resulted in incomplete conversion of **1** after 6 h; however, increasing the reaction time to 16 h resulted in complete conversion and formation of 25% of **2** and 66% of **2′** (Table 1, entries 2 & 3). Further decreasing the equivalents of H_2O_2 to either 1.5 or 1.25 resulted in longer reaction times (up to 24 h) or incomplete conversion of **1** (Table 1, entries 4–6). Therefore, we selected to move forward using 2.0 equiv. of H_2O_2 at 50 °C for 16 h as our standard reaction conditions.§ Finally, the mixture of **2** and **2′** was readily converted to pure **2** *via* saponification with a 5 M aqueous NaOH solution.

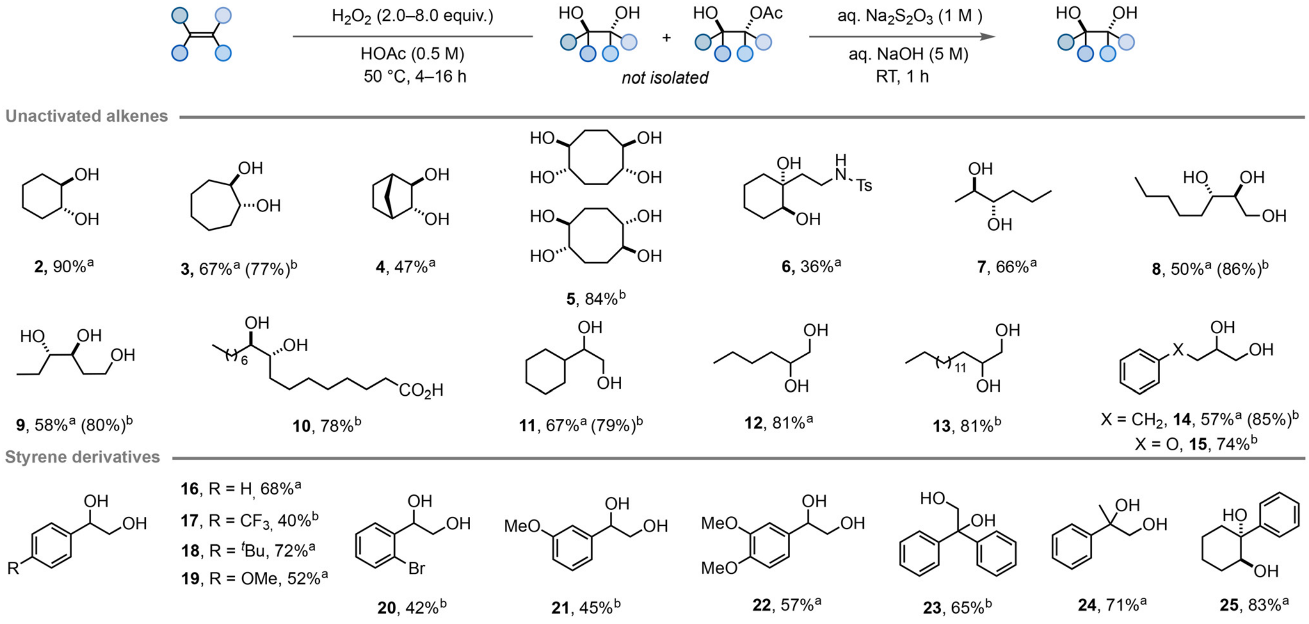
With the optimised conditions in hand, we explored the scope of the methodology (Scheme 2). For selected reactions where incomplete conversion of the starting olefin was observed, increasing the amount of H_2O_2 to 8.0 equiv. usually afforded increased yields of the targeted *anti* 1,2-diols in shorter reaction times (4 h). Cyclic alkenes can be smoothly converted to the corresponding diols (**2–6**) in moderate to excellent yields (36–84%). Interestingly, compound **6** bearing a nucleophilic tosyl-protected amine motif could be isolated in 36% yield. Meanwhile, non-cyclic internal olefins often afforded diminished yields of the vicinal diols (**7–10**) using 2.0 equiv. of H_2O_2, excellent yields (up to 86%) were obtained using 8.0 equiv. of H_2O_2. The *anti*-dihydroxylation of oleic acid proceeded smoothly under this new reaction conditions, affording the targeted diol **10** in 78% yield. Terminal olefins were also well tolerated, and the corresponding diols (**11–15**)

Table 1 Optimisation studies of dihydroxylation reactions[a]



Entry	H_2O_2 (equiv.)	*T* (°C)	*t* (h)	**1** (%)	**2** (%)	**2′** (%)
1	8.0	50	3	0	40	25
2	2.0	50	6	38	12	29
3	2.0	50	16	0	25	66
4	1.5	50	16	20	16	49
5	1.5	50	24	0	23	67
6	1.25	50	24	17	60	25

[a] Reactions were carried out on a 0.1 mmol scale. Yields determined by ^{1}H NMR using trichloroethylene as the internal standard.

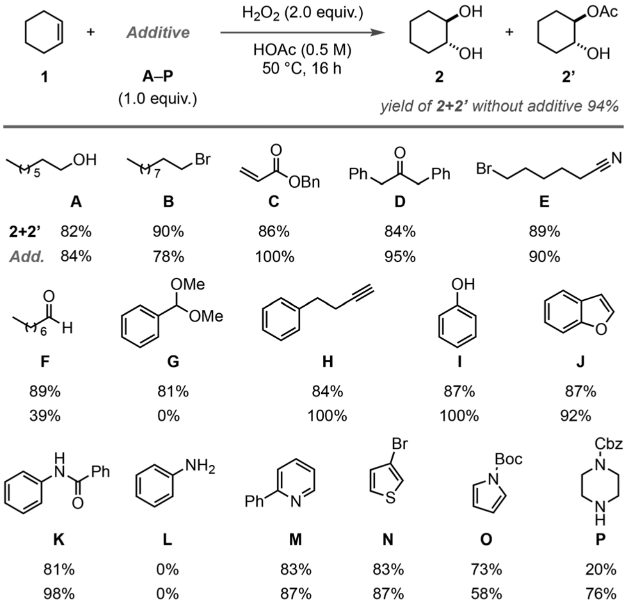


Scheme 2 Scope of the methodology. Reaction conditions: ^{a}1. alkene (0.5 mmol), H_2O_2 (2.0 equiv.), HOAc (0.5 M), 50 °C, 16 h; 2. aqueous $Na_2S_2O_3$ (1.0 M), aqueous NaOH (5.0 M), RT, 1 h. $^b H_2O_2$ (8.0 equiv.), 4 h.

were isolated in excellent yields (74–85%) using either 2.0 or 8.0 equiv. of H_2O_2.

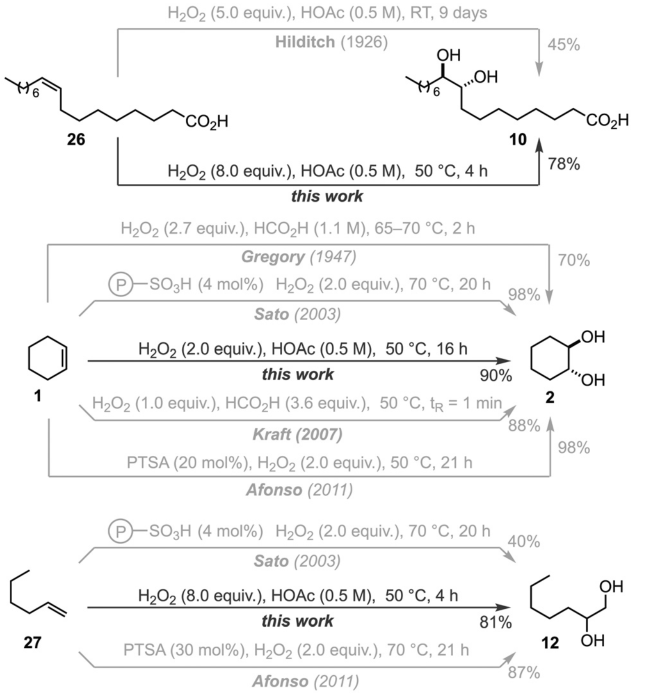
Next, we tested our protocol for the dihydroxylation of styrene derivatives (**16–25**). While styrene produced the targeted diol **16** in 68% yield, decorating the aromatic ring with electron-withdrawing groups, such as CF_3, afforded diminished yields even when 8.0 equiv. of H_2O_2 were used (**17**, 40%). The addition of electron-donating/withdrawing substituents at either the *ortho* or *meta* positions was also tolerated, and the corresponding 1,2-diols (**20–21**) were isolated in moderate yields (42–45%). The introduction of α-substituents on the styrene core was also investigated. Both α-phenylstyrene and α-methylstyrene afforded the respective diols **23** and **24** in 65% and 71% yield. Finally, dihydroxylation of 1-phenyl-1-cyclohexene yielded the *anti* 1,2-diol **25** in 83% yield.

To test the functional group compatibility of our method, we decided to conduct an additive-based screening (Scheme 3).[55–58] Cyclohexene (**1**) and equimolar amounts of a given additive (**A–P**) were subjected to the standard reaction conditions using 2.0 equiv. of H_2O_2 at 50 °C in acetic acid (0.5 M), and the outcome analysed by GC-FID using methyl laurate as the internal standard. This screening revealed that free alcohol (**A**), alkyl bromides (**B**), acrylates (**C**), ketones (**D**), nitriles (**E**), alkynes (**H**), phenols (**I**), benzofurans (**J**), benzoyl-protected anilines (**K**), pyridines (**M**) and thiophenes (**N**) are tolerated (remaining additive 78–100%) and have minimal impact on the yield of the reaction (82–90% *vs.* 94% yield without additive). While aldehydes (**F**), acetals (**G**), and Boc-protected pyrroles (**O**) are affected by our reaction conditions (remaining additive 0–58%), the targeted products **2** and **2′** could still be obtained in good yields (73–89%). However, unprotected amines (**L** and **P**) completely hamper the dihydroxylation reaction. Overall, the additive screening revealed that our method displays an excellent functional group compatibility, affording excellent yields of the targeted product, while preserving the additive in most cases.

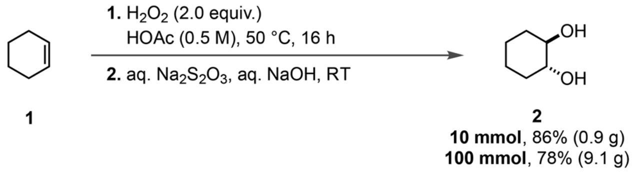


Scheme 3 Additive screening to assess the functional group tolerance of the reaction.

To evaluate how our method compares to the current state-of-the-art for the *anti*-dihydroxylation of olefins using *in situ* generated peroxy acids, we evaluated the dihydroxylation of three distinct types of olefins – internal (**26**), cyclic (**1**), and



Scheme 4 Comparison between this work and previously reported methods using *in situ* generated peroxy acids.

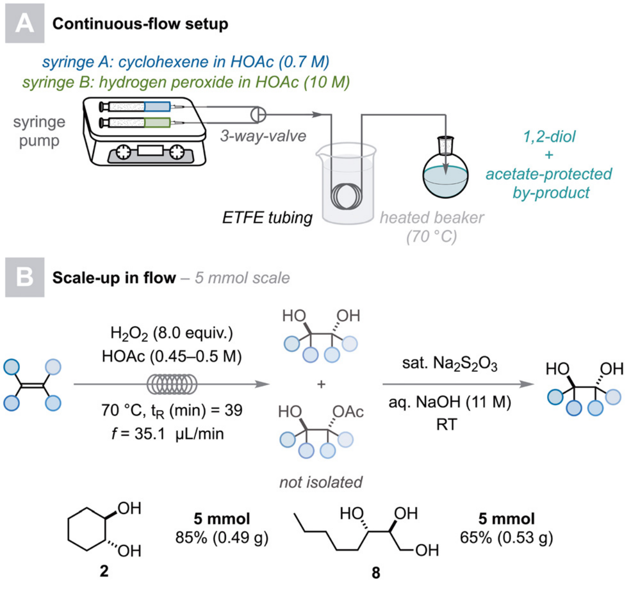


Scheme 5 Multigram-scale reactions in batch.

terminal (**27**) – using comparable methodologies (Scheme 4). For the *anti*-dihydroxylation of **26**, our conditions using 8.0 equiv. of H_2O_2 in HOAc (0.5 M) and 50 °C afforded **10** in 78% yield after 4 h, while Hilditch's original conditions yielded 45% of **10** after 9 days at room temperature.[41] For the *anti*-dihydroxylation of cyclohexene (**1**), there is more available data for comparison. Using the highly exothermic combination of formic acid and H_2O_2, Gregory obtained **2** in 70% yield after 2 h at 65–70 °C,[59] while Kraft obtained 88% of **2** after just 1 min at 50 °C using flow chemistry.[48] The combination of sulfonic acids and H_2O_2 is another popular combination for the *anti*-dihydroxylation of cyclohexene. Using a resin-bound catalyst and 2.0 equiv. of H_2O_2, Sato obtained 98% of **2** after 20 h at 70 °C;[44] while Afonso obtained 98% of **2** after 21 h combining 20 mol% of *para*-toluenesulfonic acid (PTSA) and 2.0 equiv. of H_2O_2 at 70 °C.[45] In comparison, our method afforded 90% of **2** after 16 h using 2.0 equiv. of H_2O_2 in HOAc (0.5 M) at 50 °C. Finally, for the dihydroxylation of 1-hexene (**27**), Sato's conditions afforded only 40% yield of the targeted product (**12**) after 20 h,[44] while Afonso managed to obtain 87% yield after 21 h.[45] In contrast, we were able to obtain **12** in 81% yield after 4 h using 8.0 equiv. of H_2O_2 in HOAc (0.5 M) at 50 °C. Overall, our method affords similar yields of the targeted 1,2-diols compared to reported methods using similar conditions, albeit in shorter reaction times (in batch), and bypassing the need for formic acid – and the hazards associated with it, *i.e.*, high exotherm – to generate the key peroxy acid species.

To fully exploit the applicability of this sustainable and environmentally friendly protocol, it is crucial to test its scalability (Scheme 5). First, the *anti*-dihydroxylation of cyclohexene (**1**) was carried out in 10 mmol scale. Gratifyingly, this enabled the synthesis of diol **2** in 86% yield (0.99 g) without modification of the standard reaction conditions. With this encouraging result, the reaction was further scaled up to 100 mmol scale, affording diol **2** in 78% isolated yield (9.1 g).

While these are excellent results for laboratory scale reactions, further scaling up of our process required addressing some potential safety risks. The key species in our protocol, peroxyacetic acid, is a strong oxidant and a highly reactive and corrosive species; therefore, it is desirable to avoid its use in high concentrations.[60,61] Our standard protocol enables the generation of peroxyacetic acid *in situ*, therefore circumventing hazards associated with its transport and manipulation.[61] However, for large-scale synthesis, this would still require the generation of large quantities of peroxyacetic acid, increasing potential safety risks. We hypothesised that we might be able to address these safety concerns by employing a continuous-flow process. The use of flow technology has proven beneficial in reducing reaction times while increasing safety and scalability, which is key for bulk applications in the chemical industry.[62–65] One of the main advantages offered by flow chemistry is that it enables the safe and effective use of small concentrations of highly reactive species.[12,66,67] With this in



Scheme 6 Continuous-flow setup and application.

mind, we envisioned that we might be able to exploit the low equilibrium constant for the formation of peroxyacetic acid from H_2O_2 and HOAc at room temperature to prepare a stable solution of both reagents, which would not be possible with formic acid due to the high exothermic reaction occurring when mixing it with H_2O_2.[68] This H_2O_2 solution in HOAc would mix with a solution of the alkene in HOAc at room temperature using a T-mixer. The reaction mixture would then flow through a heated coiled reactor, generating peroxyacetic acid *in situ* and enabling the targeted alkene *anti*-dihydroxylation (Scheme 6A). With this setup, only small concentrations of peroxyacetic acid would be generated at any given time, therefore decreasing the safety risks associated with the process. Using this flow protocol, we were able to prepare **2** and **8** in 5.0 mmol scale in good yields (65–85%) using a flow rate (f) of 31.5 μL min^{-1} (residence time (t_R) = 39 min) at 70 °C, and 8.0 equiv. of H_2O_2 (Scheme 6B).¶

Conclusions

In conclusion, this work demonstrates an enhanced and sustainable protocol for the *anti*-dihydroxylation of unactivated alkenes, achieved through the *in situ* formation of peroxyacetic acid. This method employs an eco-friendly and renewable solvent, acetic acid, and a relatively mild oxidant, hydrogen peroxide. This catalyst-free process exhibits a broad substrate scope with good functional group tolerance, and it is amenable to large-scale synthesis in batch (*e.g.* 100 mmol scale). Moreover, to address safety hazards associated with the generation of large quantities of highly reactive peroxyacetic acid in large-scale synthesis, a continuous flow setup for the *anti*-dihydroxylation of olefins was also developed. Overall, our protocol offers a simple, efficient, and sustainable method for the synthesis of *anti* 1,2-diols on a multigram scale.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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§ See Table S1 in the ESI† for further optimisation studies.

¶ Flow process was run under unoptimised reaction conditions.

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