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Enone Epoxidation using an isoindolinone hydroperoxide reagent inspired by a serendipitous oxazolidinone autooxidation

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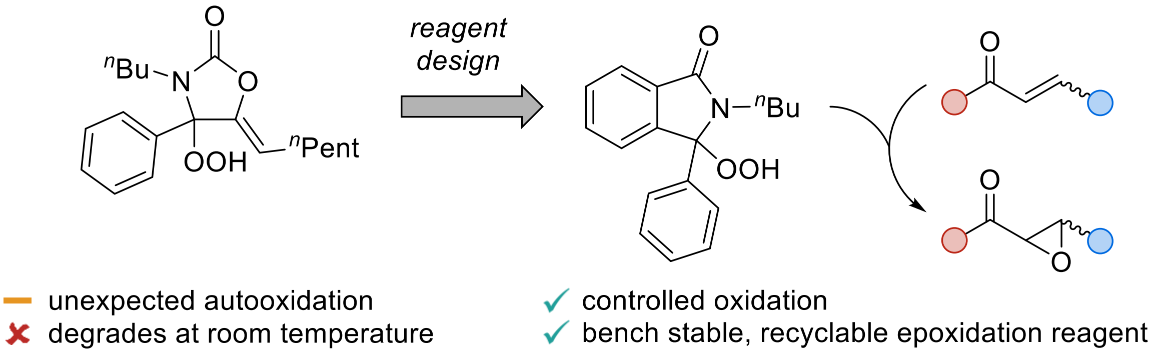
Abstract

Organic hydroperoxides are important reagents for a variety of oxidative transformations. Herein, we report the serendipitous discovery of an oxazolidinone-based hydroperoxide which was formed via autooxidation, but degraded during storage under ambient conditions. Through rational reagent design, we then developed an isoindolinone-based analog with enhanced stability (≥3 months on the benchtop). The reactivity of this hydroperoxide as an oxygen transfer reagent was demonstrated in the epoxidation of enones. Chalcones, quinones, and aliphatic cyclic enones were epoxidized in modest to excellent yields. The alcohol byproduct could be recovered, reoxidized, and reused, establishing the recyclability of this new reagent.



Keywords: Organic hydroperoxide, epoxidation, oxidant, oxazolidinone, isoindolinone, autooxidation

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Introduction

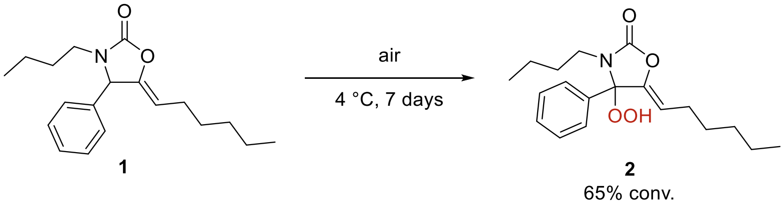
Oxidants are vital reagents in synthetic chemistry for numerous applications, including oxygen-transfer reactions,[1,2] oxidative cross-couplings,[3,4] and metal catalyst turnover.[5] While molecular oxygen and hydrogen peroxide are readily accessible and green oxidants,[6,7] further activation is often required to increase the reactivity of these reagents towards oxygen transfer.[2] Organic hydroperoxides can overcome this limitation, and heterocycle-based hydroperoxides are particularly activated due to polarization of the O–O bond caused by the heteroatoms in the ring.[2,8] A variety of nitrogen-containing and other heterocycles have been used for oxygen-transfer reactions such as (asymmetric) epoxidations of electron-deficient olefins,[8–14] Baeyer-Villiger reactions,[15] and sulfide oxidations.[10,11,16] Due to the utility of heterocycle-based hydroperoxides in organic synthesis, the further development of new reagents is of interest to the field.

Herein, we report the synthesis and reactivity of *N*-heterocycle-based hydroperoxides. We serendipitously discovered a 5-alkylidene oxazolidinone (Oxa)-based hydroperoxide which could be isolated, but readily degraded at room temperature. While we were intrigued by this motif, we sought an analog with greater stability to enable potential applications as an oxidant. Inspired by reports that isoindolinones could result in stable hydroperoxides,[9,17,18] we designed an *N*-butyl isoindolinone hydroperoxide, which was stable for ≥3 months on the benchtop. We then applied this hydroperoxide to the epoxidation of α,β-unsaturated carbonyl compounds. Chalcones, quinones, and aliphatic cyclic enones were epoxidized in modest to excellent yields whereas other types of α,β-unsaturated carbonyl compounds and electron rich alkenes did not react. The alcohol byproduct could be isolated, reoxidized, and reused for epoxidation with comparable performance. The novelty of this work lies in the unexpected autooxidation of a 5-alkylidene Oxa and the development of a new isoindolinone-based hydroperoxide as a recyclable epoxidation reagent.

Results and Discussion

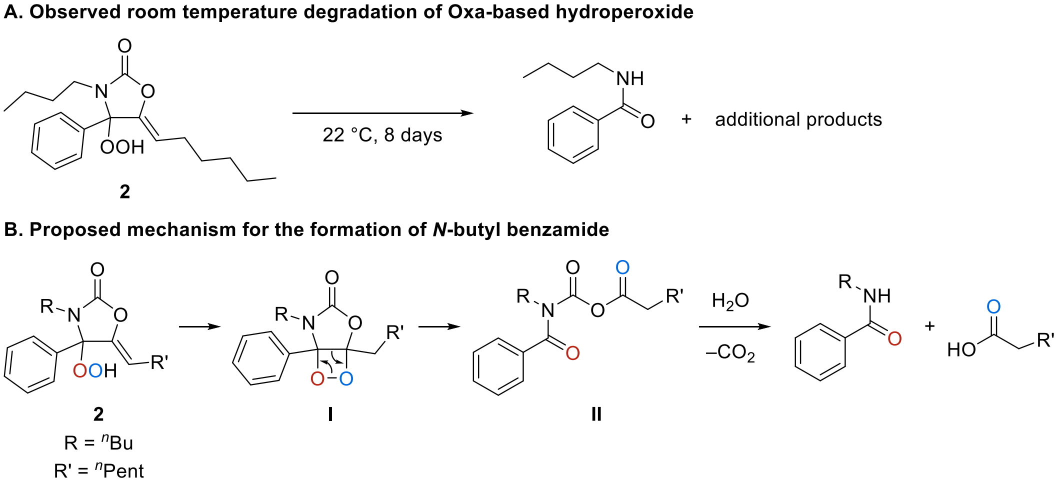
Initial observation and hydroperoxide optimization

A major focus of our group's research is advancing the synthesis, sustainability, and characterization of polyoxazolidinones (POxa),[19–21] which are an emerging subclass of polyurethanes. We were interested in expanding the scope of POxa synthesized via the four-component coupling of alkynes, aldehydes, amines, and carbon dioxide (CO_2) beyond the single example in the initial report of this methodology.[22] Starting with small molecules to facilitate reaction development, we prepared a model 5-alkylidene Oxa (**1**) which unexpectedly underwent autooxidation to a hydroperoxide (**2**) after just one week of storage at 4 °C (Scheme 1). This compound could be isolated via column chromatography and was stable for at least five weeks at 4 °C.



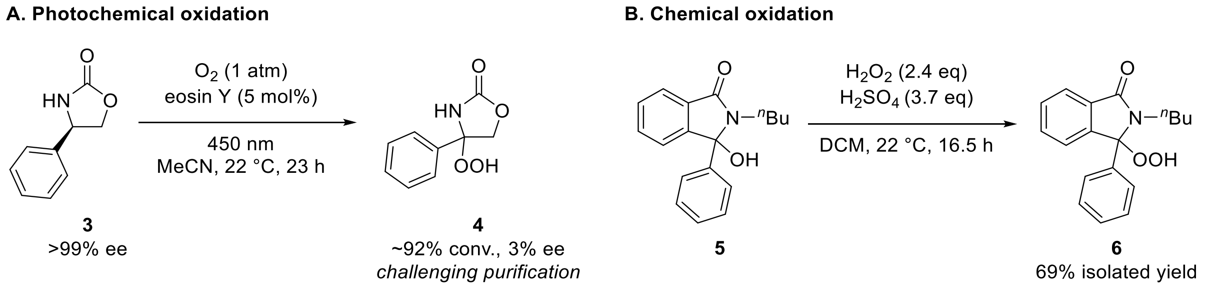
Scheme 1. Initial observation of **2**

We next attempted to optimize this oxidation under controlled conditions. Although the oxidation of **1** could be accelerated at room temperature under an oxygen atmosphere (62% conversion in 3 days), **2** partially degraded during the reaction. Despite the room temperature stability of **2** for short time scales (i.e., for column chromatography), complete degradation occurred after just eight days to form *N*-butylbenzamide and other unidentified products (Scheme 2A). We hypothesize the hydroperoxide could react with the pendent alkene to form 1,2-dioxetane intermediate **I** which could subsequently fragment to **II** (Scheme 2B). Hydrolysis would then generate CO_2, *N*-butylbenzamide, and heptanoic acid. This fragmentation-hydrolysis pathway has been reported for similar Oxa-based 1,2-dioxetanes.[23] While we were unable to identify all products or confirm this proposed mechanism, these results highlight the instability of **2**, presumably due to the allylic position of the hydroperoxide.



Scheme 2. (A) Room temperature degradation of **2** and (B) the proposed mechanism for this degradation

We, therefore, shifted our focus to *N*-heterocycles without exocyclic alkenes to improve the stability of the corresponding hydroperoxides. Additionally, we were interested in controlled oxidation methods to enable faster and more reliable synthesis than the autooxidation of **1**. Continuing with the Oxa motif, we subjected **3** to known photochemical conditions for benzylic oxidation,[24] which resulted in approximately 92% conversion to the corresponding hydroperoxide (**4**, Scheme 3A). Although **3** was enantiopure (>99% ee), the radical mechanism of this oxidation eroded the enantiomeric excess (ee) of **4** to a mere 3%. Despite the high conversion, **4** was difficult to separate from the eosin Y photosensitizer. To facilitate purification, we next explored non-photochemical conditions and identified the oxidation of alcohols to hydroperoxides using hydrogen peroxide as a promising method.[25] This approach necessitated a different heterocycle structure that contains a pendent hydroxyl group. We selected an isoindolinone (**5**) because the hydroperoxide from the oxidation of a similar structure was reported to be stable for two weeks[9] and **5** could be readily synthesized in two steps from phthalimide. Gratifyingly, **5** underwent facile oxidation to the hydroperoxide (**6**) in 69% isolated yield (Scheme 3B), which was stable at room temperature for at least three months, demonstrating a significant improvement over **2**.

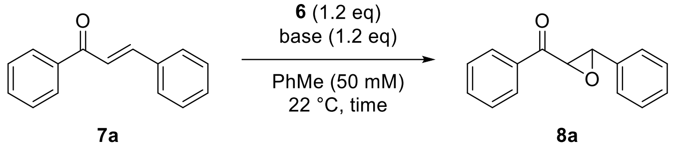


Scheme 3. Synthesis of hydroperoxides via (A) photochemical or (B) chemical oxidation

Epoxidation of α,β-Unsaturated Carbonyl Compounds

Having synthesized a bench-stable hydroperoxide, we next explored the reactivity of **6** as an oxidant. We selected the epoxidation of electron-deficient olefins (i.e., α,β-unsaturated carbonyl compounds) as a model reaction because heterocycle-based hydroperoxides are commonly used as nucleophilic epoxidation reagents.[8,9,13,14] In particular, an isoindolinone-based hydroperoxide was reported for the epoxidation of β-methyl styrene, but the scope of this reaction and further development of this reagent were not pursued.[9] The reaction conditions were optimized using *trans*-chalcone (**7a**) in toluene (PhMe; Table **1**). Reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base resulted in only 4% conversion to the epoxide (**8a**; entry 1), with moderate improvement when the time was extended to 22.5 h (33%; entry 2). Changing the base to NaOH resulted in nearly quantitative conversion in 2 h (98%; entry 3). Greater reactivity with NaOH than DBU has also been observed for epoxidations using sugar-based hydroperoxides.[13]

Table 1. Optimization of epoxidation conditions



entry	base	time (h)	conv. (%)[a]
1	DBU	2	4
2	DBU	22.5	33
3	NaOH	2	98

[a]Determined by ^1H NMR analysis of the crude reaction mixture.

Next, we explored the scope of α,β-unsaturated carbonyl compounds that are amenable to this reaction (Figure 1). Chalcone derivatives with electron withdrawing or donating substituents at the *para*-position of either aromatic ring formed epoxides **8b**–**8e** in good-to-excellent yields (72–89%). The 72% yield of **8e** is particularly noteworthy because a similar approach using a norcamphor-based hydroperoxide and *n*-butyllithium achieved only 30% yield of this more electron-rich substrate.[12] Additionally, epoxidation of 1,4-naphthoquinone afforded **8f** in 65% yield. Aliphatic cyclic enones with methyl groups at either the α- or β-position could be epoxidized to **8g**–**8h** in modest yields (11–22%). Notably, the exocyclic alkene in **8g** remained intact, highlighting the chemoselectivity of **6** for electron deficient alkenes. An α,β-unsaturated aldehyde (**7i**), anhydride (**7j**), and lactone (7**k**) were unsuccessful substrates for this transformation, even with a higher loading of base (2.6 eq) and a longer reaction time (22.5 h). *Trans*-cinnamaldehyde **7i**, in particular, is known to be a challenging substrate for epoxidation with heterocycle-based hydroperoxides.[8]

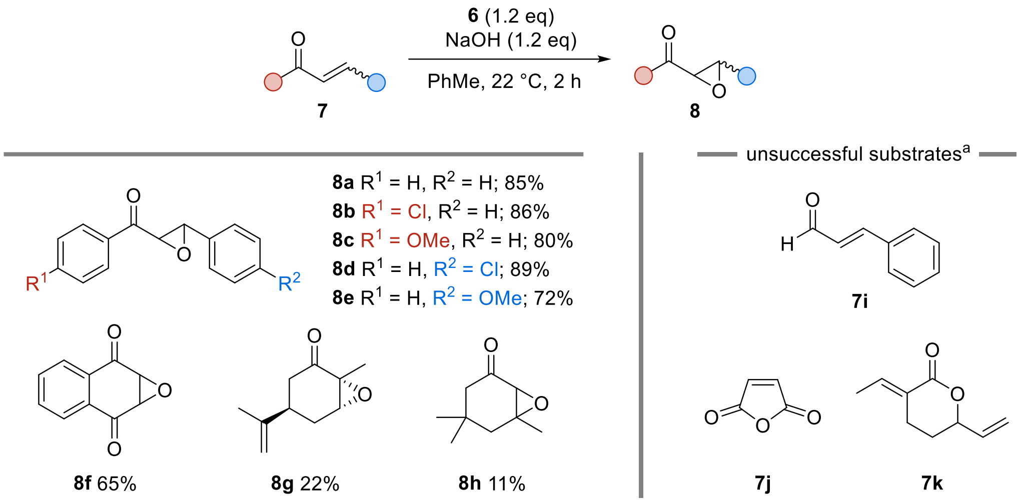


Figure 1. Epoxidation scope of α,β-unsaturated carbonyl compounds. Standard reaction conditions: alkene (0.20 mmol, 1.0 eq), **6** (0.24 mmol, 1.2 eq), NaOH (0.24 mmol, 1.2 eq), PhMe (50 mM), 22 °C, 2 h. Isolated yields. [a]Conducted on a 0.015 mmol scale with 2.6 eq NaOH for 22.5 h.

The epoxidation of enones with hydroperoxides has been reported[12] to proceed via a conjugate addition followed by an intramolecular S_N2 to form the epoxide and generate an alcohol byproduct (i.e., **5** in our system). This byproduct (along with unreacted **6** for some substrates) could be readily recovered in 88–97% yield and reoxidized to **6**. The percent recovery of **5** is similar to the alcohol byproduct of norcamphor-based hydroperoxides (95%)[12] and higher than for the hemiacetal byproduct of sugar-based hydroperoxides (0–80%),[13] likely due to the greater stability of the isoindolinone motif. Both newly synthesized and recycled **6** performed comparably in the epoxidation of **7a** (Figure 2), demonstrating the recyclability of this reagent.

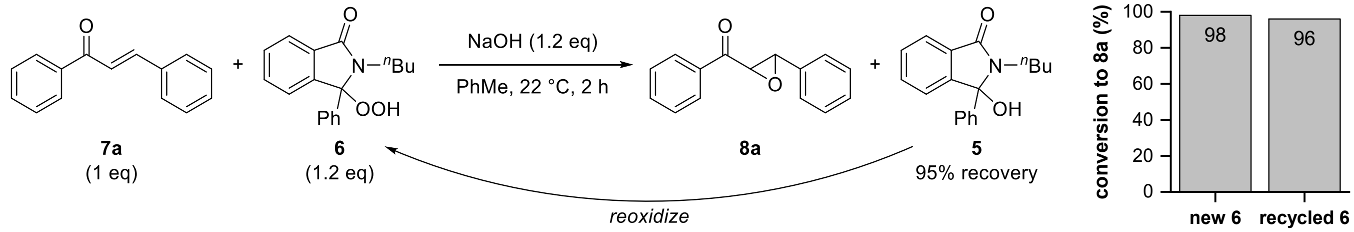


Figure 2. Recyclability of **6** in the epoxidation of **7a**.

Conclusions

In summary, we serendipitously discovered the autooxidation of a 5-alkylidene Oxa to the corresponding hydroperoxide. This compound could be isolated, but degraded during storage at room temperature, which we attribute to intramolecular reactivity of the hydroperoxide with the exocyclic alkene. Careful design of the *N*-heterocycle and optimization of oxidation conditions yielded a bench-stable isoindolinone-based hydroperoxide. We then demonstrated the application of this hydroperoxide in the epoxidation of enones.

Chalcone derivatives with electron withdrawing and donating substituents as well as 1,4-naphthoquinone were epoxidized in good-to-excellent yields. Aliphatic cyclic enones with α- or β-methyl groups were also viable substrates, although with modest yields. The epoxidation proceeded chemoselectively for the enone in the presence of more electron-rich alkenes. Additionally, the alcohol byproduct could be recovered in excellent yield, reoxidized, and reused with comparable results. This work provides a new, bench-stable hydroperoxide as a recyclable reagent for the chemoselective epoxidation of enones.

Experimental Section

Methods and Instruments.

Unless otherwise stated, all synthetic manipulations were carried out in air. Flash-column chromatography was performed with silica gel (particle size 3–200 µm, 70–320 mesh) using mixtures of ethyl acetate (EtOAc) and hexanes. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher and Sigma Aldrich).

NMR spectra were recorded on a Bruker 400 MHz Avance III HD instrument with a BBO SmartProbe [(^{1}H, 400 MHz), (^{13}C, 101 MHz)] or a Bruker 500 MHz Avance III HD instrument with a Prodigy TCI cryoprobe [(^{1}H, 500 MHz), (^{13}C, 126 MHz)] at 22 °C with shifts reported relative to the residual solvent peak [$CDCl_3$: 7.26 ppm (^{1}H), 77.16 ppm (^{13}C)]. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = hextet, sep = septet, m = multiplet), coupling constants (in Hz), and integration. Deuterated chloroform was purchased from Cambridge Isotope Laboratories and stored over 3 Å molecular sieves.

High-resolution mass spectrometry (HRMS) analyses were performed on a Sciex X500R UPLC/QTOF-MS instrument using a positive tune mix (Sciex part number 5042912) as an external calibrant.

High-performance liquid chromatography (HPLC) analyses were performed on a Shimadzu Prominence-i LC-2030C 3D instrument using a Daicel Chiracel OD-3 column (4.6 x 150 mm, 3 µm pore size), isopropanol/hexanes = 5/95 as the eluent at a flow rate of 1 mL/min, and a detection wavelength of 190 nm.

Sources of Reagents and Solvents

Tetrahydrofuran (THF) was purchased from Fisher, sparged with argon, passed through two packed columns of neutral alumina, and then degassed by three freeze-pump-thaw cycles prior to first use. 3-Ethyl-6-vinyltetrahydro-2*H*-pyran-2-one (**7k**) was provided by Dr. Rachel Rapagnani and was prepared following a published procedure.[26] Phenyllithium (1.9 M in dibutyl ether) was purchased from Sigma-Aldrich. CO_2 (bone dry) was purchased from Airgas and used as received. All other solvents and reagents were purchased from Sigma-Aldrich, TCI, Oakwood, Alfa Aesar, Fluka, or Eastman Kodak and used as received.

Synthetic Procedures

(*Z*)-3-Butyl-5-hexylidene-4-phenyloxazolidin-2-one (1). Adapted from a literature procedure,[22] copper(I) iodide (549 mg, 2.88 mmol, 0.3 eq) was added to a flame-dried 2-dram vial under N_2. Benzaldehyde (1.00 mL, 9.74 mmol, 1 eq), butylamine (967 µL, 9.74 mmol, 1 eq), and 1-heptyne (1.30 mL, 9.74 mmol, 1 eq) were added. The vial was then quickly uncapped and placed in a custom 6-well high-pressure reactor[27] and the headspace was purged 3x with CO_2 before pressurizing to 100 psig. The reaction was stirred at 75 °C for 25 h, then cooled in dry ice before slowly venting. The crude reaction mixture was purified by two silica gel columns (in 1:20 to 1:10 then in 1:20 EtOAc:hexanes) to give **1** as a yellow oil (642 mg, 2.53 mmol, 26% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 3H), 7.30–7.23 (m, 2H), 5.20 (q, *J* 1.8 Hz, 1H), 4.34 (td, *J* 7.6, 2.1 Hz, 1H), 3.50–3.38 (m, 1H), 2.81–2.70 (m, 1H), 2.19–2.00 (m, 2H), 1.47–1.36 (m, 2H), 1.36–1.13 (m, 8H), 0.85 (dt, *J* 7.2, 4.7 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.7, 147.3, 138.2, 129.2, 129.1, 127.8, 105.0, 62.8, 41.6, 31.4, 29.1, 29.0, 24.9, 22.5, 19.9, 14.1, 13.7. **HRMS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{28}NO_2^+$ 302.2114; found 302.2140.

(*Z*)-3-Butyl-5-hexylidene-4-hydroperoxy-4-phenyloxazolidin-2-one (2). 1 (137 mg, 0.455 mmol) was placed in a sealed 20 mL vial under air in a refrigerator (4 °C) for storage. After 7 days, we observed the contents of the vial had solidified, indicating **1** had undergone unexpected autooxidation to **2**. The crude product was purified by silica gel chromatography (1:4 EtOAc:hexanes) to give **2** as a white solid (34.5 mg, 0.103 mmol, 23% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.52–7.46 (m, 3H), 7.45–7.40 (m, 2H), 4.57 (dd, *J* 8.3, 6.8 Hz, 1H), 3.63–3.44 (m, 2H), 1.81–1.65 (m, 2H), 1.55–1.40 (m, 2H), 1.35–1.12 (m, 8H), 0.83 (t, *J* 7.2 Hz, 3H), 0.78 (t, *J* 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.6, 133.9, 130.2, 129.9, 129.1, 129.0, 126.0, 78.2, 42.2, 31.5, 30.6, 29.7, 25.4, 22.5, 19.7, 14.1, 13.6. **HRMS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{28}NO_4^+$ 334.2013; found 334.2016.

4-Hydroperoxy-4-phenyloxazolidin-2-one (4). 3 (6.5 mg, 0.040 mmol, 1 eq) was dissolved in acetonitrile (200 uL) in a septa-capped 1-dram vial. Eosin Y (1.5 mg, 0.0022 mmol, 0.054 eq) and an O_2 balloon were added and the headspace was purged for ~5 min. The reaction was placed in an EvoluChem PhotoRedOx Box equipped with EvoluChem 18W 450 nm LED bulbs. The embedded cooling fan in the box was powered and the whole box was placed on a magnetic stirrer. The reaction was stirred under irradiation for 23 h, then a crude aliquot was taken for analysis by ^{1}H NMR spectroscopy (approximately 92% conv. based on the ratio of peak integrations between **3** and **4**) and HPLC (3% ee). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.44–7.40 (m, 2H), 7.39–7.34 (m, 3H), 6.53 (s, 1H), 4.72 (d, *J* 10.0 Hz, 1H), 4.23 (d, *J* 10.0 Hz, 1H). **HPLC** (Chiracel OD-3, isopropanol/hexanes = 5/95, 1.0 mL/min, 190 nm) retention time 11.71 min (*S*-enantiomer, 51.5%), 19.61 min (*R*-enantiomer, 48.5%). The enantiomer assignments are putative based on the elution order of the starting material.

2-Butylisoindoline-1,3-dione. Adapted from a literature procedure,[28] phthalimide (738 mg, 5.02 mmol, 1 eq) and potassium carbonate (1.38 g, 10.0 mmol, 2 eq) were added to an oven-dried 25 mL Schlenk flask under N_2 and suspended in anhydrous *N*,*N*-dimethylformamide (4.3 mL). 1-Bromobutane (1.08 mL, 10.0 mmol, 2 eq) was added and the reaction was stirred at 40 °C for 25 h then diluted with EtOAc (25 mL) and washed with 10% aqueous LiCl (5x5 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to give the title compound as a pale yellow oil, which was used without further purification (846 mg, 4.16 mmol, 83% yield). Spectral data match literature values.[28] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86–7.79 (m, 2H), 7.72–7.67 (m, 2H), 3.68 (t, *J* 7.4 Hz, 2H), 1.70–1.60 (m, 2H), 1.36 (h, *J* 7.4 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.6, 133.9, 132.3, 123.3, 37.9, 30.8, 20.2, 13.8.

2-Butyl-3-hydroxy-3-phenylisoindolin-1-one (5). Adapted from a literature procedure,[29] 2-butylisoindoline-1,3-dione (506 mg, 2.47 mmol, 1 eq) was added to an oven-dried 100 mL Schlenk flask under N_2, dissolved in anhydrous THF (25 mL), and cooled to 0 °C. Phenyl lithium (1.9 M in dibutyl ether, 1.6 mL, 3.0 mmol, 1.2 eq) was added dropwise. The reaction was slowly warmed to 22 °C and stirred for 19.5 h then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0 to 100% EtOAc in hexanes) to give **5** as a white solid (555 mg, 1.98 mmol, 80% yield). Spectral data match literature values.[30] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69–7.61 (m, 1H), 7.48–7.40 (m, 1H), 7.40–7.33 (m, 3H), 7.32–7.26 (m, 3H), 7.26–7.21 (m, 1H), 3.78 (s, 1H), 3.36 (ddd, *J* 13.9, 9.7, 5.9 Hz, 1H), 2.89 (ddd, *J* 13.9, 9.7, 5.8 Hz, 1H), 1.47–1.34 (m, 1H), 1.32–1.21 (m, 1H), 1.15 (h, *J* 7.2 Hz, 2H), 0.76 (t, *J* 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.0, 149.1, 138.8, 132.6, 130.7, 129.5, 128.6, 128.5, 126.3, 123.3, 122.8, 91.5, 39.5, 30.9, 20.6, 13.8.

2-Butyl-3-hydroperoxy-3-phenylisoindolin-1-one (6). Adapted from a literature procedure,[31] **5** (513 mg, 1.82 mmol, 1 eq) was dissolved in dichloromethane (DCM, 9.1 mL) in a 20 mL vial and cooled in an ice bath.

Concnetrated sulfuric acid (360 µL, 6.75 mmol, 3.7 eq) then hydrogen peroxide (30% in H_2O, 450 µL, 4.41 mmol, 2.4 eq) were added dropwise. The reaction was slowly warmed to 22 °C and stirred for 16.5 h then washed with saturated aqueous Na_2CO_3 and brine. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by crystallization from DCM/hexanes at 0 °C to give **6** as a white solid (372 mg, 1.25 mmol, 69% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.84–7.77 (m, 1H), 7.48 (pd, *J* 7.4, 1.4 Hz, 2H), 7.38–7.31 (m, 5H), 7.30–7.27 (m, 1H), 3.51 (ddd, *J* 14.0, 10.3, 5.6 Hz, 1H), 3.12 (ddd, *J* 14.0, 10.3, 5.6 Hz, 1H), 1.61–1.38 (m, 2H), 1.33–1.15 (m, 2H), 0.82 (t, *J* 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.1, 145.0, 135.8, 132.5, 132.3, 129.9, 129.3, 128.9, 126.3, 123.4, 122.7, 100.1, 39.9, 30.6, 20.6, 13.8. **HRMS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}NO_3^+$ 298.1438; found 298.1446.

General procedure A. Substituted chalcone synthesis

Adapted from a literature procedure,[32] the (substituted) acetophenone (2.5 mmol, 1 eq) and (substituted) benzaldehyde (2.5 mmol, 1 eq) were added to a 20 mL vial, dissolved in ethanol (EtOH, 5 mL, 500 mM), and cooled to 0 °C. NaOH (20% in H_2O, 312 µL, 0.95 eq) was added dropwise and the reaction was stirred at 22 °C for the indicated time. The crude chalcone was recrystallized from EtOH then washed with cold EtOH and water.

4′-Chlorochalcone (7b). Following General Procedure A, 4′-chloroacetophenone (325 µL, 2.50 mmol, 1 eq) and benzaldehyde (257 µL, 2.50 mmol, 1 eq) were reacted for 90 min to give **7b** as a white solid (295 mg, 1.22 mmol, 49% yield). Spectral data match literature values.[33] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00–7.94 (m, 2H), 7.82 (d, *J* 15.7 Hz, 1H), 7.68–7.61 (m, 2H), 7.53–7.46 (m, 3H), 7.46–7.40 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 189.3, 145.5, 139.4, 136.7, 134.9, 130.9, 130.1, 129.2, 129.1, 128.7, 121.7.

4′-Methoxychalcone (7c). Following General Procedure A, 4′-methoxyacetophenone (379 mg, 2.50 mmol, 1 eq) and benzaldehyde (257 µL, 2.50 mmol, 1 eq) were reacted for 90 min to give **7c** as a white solid (442 mg, 1.85 mmol, 74% yield). Spectral data match literature values.[33] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08–8.02 (m, 2H), 7.81 (d, *J* 15.7 Hz, 1H), 7.69–7.61 (m, 2H), 7.55 (d, *J* 15.6 Hz, 1H), 7.46–7.37 (m, 3H), 7.02–6.96 (m, 2H), 3.90 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 188.9, 163.6, 144.1, 135.2, 131.3, 131.0, 130.5, 129.1, 128.5, 122.1, 114.0, 55.7.

4-Chlorochalcone (7d). Following General Procedure A, acetophenone (292 µL, 2.50 mmol, 1 eq) and 4-chlorobenzaldehyde (351 mg, 2.50 mmol, 1 eq) were reacted for 10 min to give **7d** as a pale yellow solid (196 mg, 0.808 mmol, 32% yield). Spectral data match literature values.[33] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05–7.99 (m, 2H), 7.76 (d, *J* 15.7 Hz, 1H), 7.63–7.55 (m, 3H), 7.55–7.47 (m, 3H), 7.43–7.37 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 190.4, 143.5, 138.2, 136.6, 133.5, 133.1, 129.7, 129.4, 128.8, 128.6, 122.6.

4-Methoxychalcone (7e). Following General Procedure A, acetophenone (292 µL, 2.50 mmol, 1 eq) and *p*-anisaldehyde (312 µL, 2.50 mmol, 1 eq) were reacted for 22 h to give **7e** as a pale yellow solid (183 mg, 0.768 mmol, 31% yield). Spectral data match literature values.[33] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05–7.99 (m, 2H), 7.79 (d, *J* 15.6 Hz, 1H), 7.64–7.55 (m, 3H), 7.54–7.47 (m, 2H), 7.42 (d, *J* 15.6 Hz, 1H), 6.98–6.91 (m, 2H), 3.86 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 190.8, 161.8, 144.9, 138.7, 132.7, 130.4, 128.7, 128.6, 127.8, 112.0, 114.6, 55.6.

General procedure B. Epoxidation

Alkene substrates **7a** and **7f**–**7j** were purchased from Sigma-Aldrich, Alfa Aesar, Fluka, or Eastman Kodak and used as received. Adapted from a literature procedure,[13] **6** (0.24 mmol, 1.2 eq) was dissolved in toluene (4.0 mL) in a 20 mL vial. Freshly ground NaOH (0.24 mmol, 1.2 eq) was added and the reaction was stirred at 22 °C for 10 min before the alkene substrate was added (0.20 mmol, 1 eq). The reaction was stirred at 22 °C for an additional 2 h then diluted with EtOAc (20 mL) and washed with H_2O (3x5 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography in mixtures of EtOAc and hexanes.

Phenyl(3-phenyloxiran-2-yl)methanone (8a). Following General Procedure B, chalcone (41.7 mg, 0.200 mmol, 1 eq) was reacted with **6** (71.2 mg, 0.240 mmol, 1.2 eq) and NaOH (9.9 mg, 0.25 mmol, 1.2 eq). Purification by silica gel chromatography (1:30 to 1:1 EtOAc:hexanes) gave **8a** as a white solid (37.9 mg, 0.169 mmol, 85% yield) and **5** as a white solid (64.1 mg, 0.228 mmol, 95% recovery). Spectral data for **8a** match literature values.[34] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05–7.99 (m, 2H), 7.63 (tt, *J* 7.4, 1.3 Hz, 1H), 7.50 (t, *J* 7.8 Hz, 2H), 7.46–7.35 (m, 5H), 4.30 (d, *J* 1.9 Hz, 1H), 4.09 (d, *J* 1.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.2, 135.6, 134.2, 129.2, 129.1, 129.0, 128.9, 128.5, 125.9, 61.2, 59.5.

(4-Chlorophenyl)(3-phenyloxiran-2-yl)methanone (8b). Following General Procedure B, **7b** (48.4 mg, 0.200 mmol, 1 eq) was reacted with **6** (71.2 mg, 0.240 mmol, 1.2 eq) and NaOH (9.7 mg, 0.25 mmol, 1.2 eq). Purification by silica gel chromatography (1:30 to 1:1 EtOAc:hexanes) gave **8b** as a white solid (44.6 mg, 0.172 mmol, 86% yield) and **5** as a white solid (61.4 mg, 0.218 mmol, 91% recovery). Spectral data for **8b** match literature values.[34] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (d, *J* 8.6 Hz, 2H), 7.47 (d, *J* 8.6 Hz, 2H), 7.44–7.33 (m, 5H), 4.23 (d, *J* 1.9 Hz, 1H), 4.08 (d, *J* 1.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.2, 140.8, 135.4, 133.9, 130.0, 129.4, 129.3, 129.0, 125.9, 61.2, 59.5.

(4-Methoxyphenyl)(3-phenyloxiran-2-yl)methanone (8c). Following General Procedure B, **7c** (47.7 mg, 0.200 mmol, 1 eq) was reacted with **6** (71.3 mg, 0.240 mmol, 1.2 eq) and NaOH (9.5 mg, 0.24 mmol, 1.2 eq). Purification by silica gel chromatography (1:10 to 1:1 EtOAc:hexanes) gave **8c** as a colorless oil (40.7 mg, 0.158 mmol, 80% yield) and **5** as a white solid (63.3 mg, 0.225 mmol, 94% recovery). Spectral data for **8c** match literature values.[34] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* 8.9 Hz, 2H), 7.44–7.34 (m, 5H), 6.97 (d, *J* 8.9 Hz, 2H), 4.25 (d, *J* 1.9 Hz, 1H), 4.07 (d, *J* 1.9 Hz, 1H), 3.88 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.5, 164.4, 135.9, 130.9, 129.1, 128.9, 128.8, 125.9, 114.2, 61.0, 59.3, 55.7.

(3-(4-Chlorophenyl)oxiran-2-yl)(phenyl)methanone (8d). Following General Procedure B, **7d** (48.4 mg, 0.200 mmol, 1 eq) was reacted with **6** (71.2 mg, 0.240 mmol, 1.2 eq) and NaOH (9.4 mg, 0.24 mmol, 1.2 eq). Purification by silica gel chromatography (1:30 to 1:1 EtOAc:hexanes) gave **8d** as a white solid (46.2 mg, 0.179 mmol, 89% yield) and **5** as a white solid (61.8 mg, 0.220 mmol, 92% recovery). Spectral data for **8d** match literature values.[34] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04–7.98 (m, 2H), 7.63 (dt, *J* 7.4, 1.3 Hz, 1H), 7.49 (t, *J* 7.8 Hz, 2H), 7.38 (d, *J* 8.5 Hz, 2H), 7.31 (d, *J* 8.5 Hz, 2H), 4.25 (d, *J* 1.9 Hz, 1H), 4.06 (d, *J* 1.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.9, 135.5, 135.1, 134.3, 134.2, 129.2, 129.1, 128.5, 127.3, 61.1, 58.8.

(3-(4-Methoxyphenyl)oxiran-2-yl)(phenyl)methanone (8e). Following General Procedure B, **7e** (47.6 mg, 0.200 mmol, 1 eq) was reacted with **6** (71.4 mg, 0.240 mmol, 1.2 eq) and NaOH (9.4 mg, 0.24 mmol, 1.2 eq). Purification by silica gel chromatography (1:20 to 1:1 EtOAc:hexanes) gave **8e** as a yellow solid (36.6 mg, 0.144 mmol, 72% yield) and **5** as a white solid (65.4 mg, 0.232 mmol, 97% recovery). Spectral data for **8e** match literature values.[34] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04–7.98 (m, 2H), 7.62 (dt, *J* 7.4, 1.3 Hz, 1H), 7.49 (d, *J* 7.7 Hz, 2H), 7.30 (d, *J* 8.7 Hz, 2H), 6.93 (d, *J* 8.7 Hz, 2H), 4.29 (d, *J* 1.9 Hz, 1H), 4.03 (d, *J* 1.9 Hz, 1H), 3.83 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.4, 160.5, 135.7, 134.1, 129.0, 128.5, 127.5, 127.3, 114.4, 61.2, 59.5, 55.5.

1a,7a-Dihydronaphtho[2,3-b]oxirene-2,7-dione (8f). Following General Procedure B, 1,4-naphthoquinone (32.8 mg, 0.200 mmol, 1 eq) was reacted with **6** (71.2 mg, 0.240 mmol, 1.2 eq) and NaOH (9.5 mg, 0.24 mmol, 1.2 eq). Purification by silica gel chromatography (1:20 to 1:1 EtOAc:hexanes) gave **8f** as an off white solid (22.6 mg, 0.130 mmol, 65% yield), **5** as a white solid (48.1 mg, 0.171 mmol, 71% recovery), and **6** as a white solid (12.0 mg, 0.0404 mmol, 17% recovery). Spectral data for **8f** match literature values.[35] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.78 (m, 2H), 4.03 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 190.9, 134.9, 131.9, 127.4, 55.5.

(1*R*,4*R*,6*R*)-1-Methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-one (8g). Following General Procedure B, *R*-(−)-carvone (32 µL, 0.20 mmol, 1 eq) was reacted with **6** (71.4 mg, 0.240 mmol, 1.2 eq) and NaOH (9.6 mg, 0.24 mmol, 1.2 eq). Purification by silica gel chromatography (1:40 to 1:1 EtOAc:hexanes) gave **8g** as a colorless oil (7.3 mg, 0.044 mmol, 22% yield) and **5** as a white solid (59.7 mg, 0.212 mmol, 88% recovery). The diastereomer of **8g** was assigned by comparison to the reported NMR spectra for the same isomer.[36] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.79 (s, 1H), 4.71 (s, 1H), 3.44 (d, *J* 3.1 Hz, 1H), 2.72 (tt, *J* 11.1, 4.6 Hz, 1H), 2.58 (dd, *J* 17.7, 4.5 Hz, 1H), 2.37 (dt, *J* 14.9, 3.8 Hz, 1H), 2.02 (ddd, *J* 17.6, 11.6, 1.4 Hz, 1H), 1.90 (dd, *J* 14.8, 11.1 Hz, 1H), 1.71 (s, 3H), 1.41 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.6, 146.5, 110.6, 61.5, 59.0, 41.9, 35.2, 28.9, 20.7, 15.4.

4,4,6-Trimethyl-7-oxabicyclo[4.1.0]heptan-2-one (8h). Following General Procedure B, isophorone (31 µL, 0.20 mmol, 1 eq) was reacted with **6** (71.5 mg, 0.240 mmol, 1.2 eq) and NaOH (9.6 mg, 0.24 mmol, 1.2 eq). Purification by silica gel chromatography (1:15 to 1:1 EtOAc:hexanes) gave **8h** as a yellow oil (3.5 mg, 0.022 mmol, 11% yield), **5** as a white solid (28.2 mg, 0.100 mmol, 42% recovery), and **6** as a white solid (37.8 mg, 0.127 mmol, 53% recovery). Spectral data for **8h** match literature values.[37] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.05 (s, 1H), 2.62 (dd, *J* 13.3, 1.0 Hz, 1H), 2.08 (dd, *J* 13.3, 1.0 Hz, 1H), 1.81 (ddd, *J* 13.3, 2.2, 1.1 Hz, 1H), 1.69 (dd, *J* 14.9, 2.2 Hz, 1H), 1.42 (s, 3H), 1.02 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.2, 64.5, 61.6, 48.2, 42.9, 36.4, 31.0, 28.0, 24.2.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of new compounds and HPLC chromatograms are available in the Supplementary Material file associated with this paper.

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