

Kinetic Resolution in Asymmetric Epoxidation using Iminium Salt Catalysis

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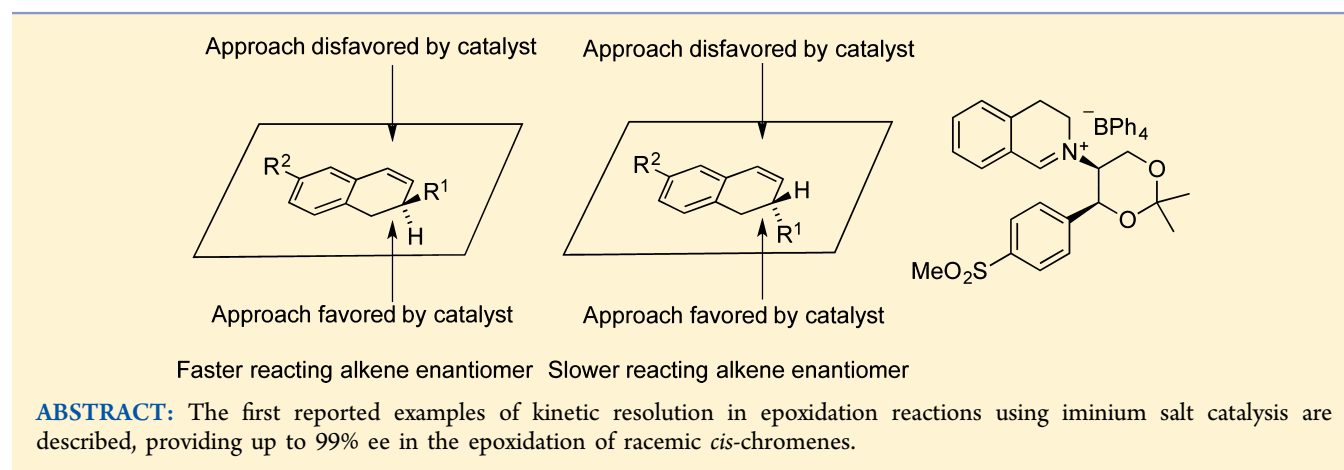
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Supporting Information



INTRODUCTION

Asymmetric epoxidation of alkenes to generate optically active epoxides is an extremely powerful synthetic tool,¹ and the development of effective organocatalytic systems for epoxidation has received considerable attention.² The most successful organocatalytic methods for epoxidation are those utilizing dioxiranes and those utilizing oxaziridinium salts. Chiral ketones, precursors to dioxiranes, such as those of Yang,³ Denmark,⁴ Armstrong,⁵ and Shi,⁶ have achieved high enantioselectivities, with observed values of up to 97% ee. Oxaziridinium salts, first reported by Lusinchi in 1976,⁷ are also reactive reagents for oxygen transfer to nucleophilic substrates, such as sulfides and alkenes, and may be generated catalytically by use of iminium salts in the presence of a stoichiometric oxidant, typically oxone.⁸

We have developed a range of catalysts for epoxidation reactions based on biphenylazepinium (e.g., **1**), binaphthylazepinium (e.g., **2**), and dihydroisoquinolinium (e.g., **3**) moieties containing a chiral appendage on the nitrogen atom, with the most successful to date containing the 1,3-dioxane motif (Figure 1).⁹ We have also shown that alternative oxidants may be used in iminium salt-catalyzed epoxidation reactions, such as hydrogen peroxide,¹⁰ sodium hypochlorite,¹¹ and electrochemically generated oxidants.¹² Amines have also been used as

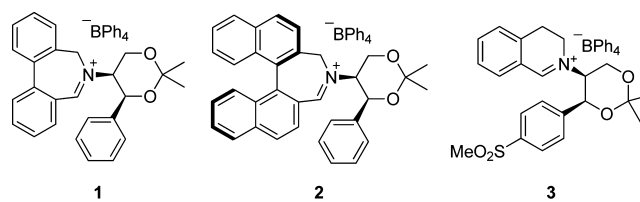


Figure 1. Iminium salt catalysts.

iminium precursors in similar epoxidation processes by us¹³ and others.¹⁴

We reported the first very high enantioselectivities in the asymmetric epoxidation of alkenes using iminium salt catalysts, and we have developed nonaqueous conditions for these processes using tetraphenylphosphonium monoperoxysulfate (TPPP)¹⁵ as the oxidant.¹⁶ We have used the process, for example, in the syntheses of levromakalim **4**,¹⁷ (–)-lomatin **5** and (+)-*trans*-khellactone **6**,¹⁸ and scuteflorin,¹⁹ utilizing iminium salt catalysts **1** and **3** (Figure 2). Kinetic resolution in these iminium salt-catalyzed epoxidation processes has not

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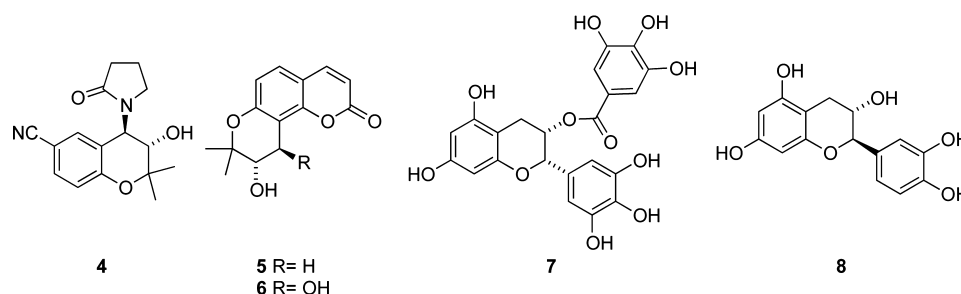


Figure 2. Levcromakalim, lomatatin, khellactone, epigallocatechin-3-gallate, and catechin.

been reported, and given the high levels of enantioselectivities observed in the epoxidation of 2-substituted benzopyrans under our conditions, we decided to evaluate these substrates as possible candidates for kinetic resolution using iminium salt catalyst **3**, the most enantioselective for chromene substrates. This core structure is also found in a range of natural products, including a number of flavonoids isolated from green tea extracts (up to 40% of the dry weight),²⁰ such as epigallocatechin-3-gallate (EGCG) **7** and catechin **8**.

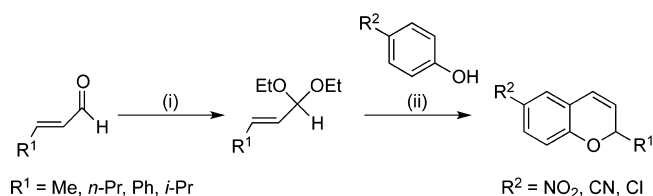
RESULTS AND DISCUSSION

Kinetic resolution of racemic alkenes using asymmetric epoxidation is an attractive topic for asymmetric catalysis, as racemic alkenes are generally cheap and readily available, but is potentially more challenging than the asymmetric epoxidation of prochiral alkenes. Kinetic resolution in asymmetric epoxidation has been observed previously by Sharpless,²¹ Jacobsen,²² Katsuki,²³ and Shi.²⁴

We report herein the first successful demonstration of iminium salt-catalyzed epoxidation as a tool for kinetic resolution of 2-substituted benzopyrans. A number of procedures have been reported to achieve the synthesis of 2*H*-chromenes, including inter alia: via an allene intermediate through a Claisen rearrangement,²⁵ oxidation of allylphenols,²⁶ iodination of allylphenols,²⁷ using metal phenoxides and carbonyls,²⁸ using palladium catalysis,²⁹ dehydration of chromenols,³⁰ using the Wittig reaction,³¹ using metathesis,³² and using the Petasis reaction.³³ Substrates **13a–13c**, **14a–14c**, **15a–15c**, and **16a–16c**, containing the benzopyran core structure, were prepared quickly by us in two steps using the procedure reported by North.³⁴ This route allows easy variation of substituents at both the C2 and the C6 positions of the chromenes using the corresponding dialkylacetals and phenols. We have found diethyl acetals **9–12** to be the most reactive substrates for this reaction, the dimethyl acetals being much less reactive. The diethyl acetals were prepared from the corresponding aldehydes in good yields and were subsequently reacted with 4-chloro-, 4-cyano-, and 4-nitro-phenol to give the corresponding chromenes **13–16** (Scheme 1, Table 1).

The chromenes were submitted to standard epoxidation reaction conditions using *m*-CPBA (Scheme 2, Table 2). Diastereoisomeric ratios (*trans*:*cis*) for the epoxide products were obtained using ¹H NMR spectroscopy carried out on the inseparable mixture of diastereoisomers, and ranged from 1:1 to exclusively *trans* with increasing bulk of the R¹ substituent at C2. Decomposition was observed when chromenes containing a chloro R² substituent at C6 were submitted to the epoxidation conditions; neither the epoxides nor the corresponding diols were isolated from the reaction mixtures.

Scheme 1^a

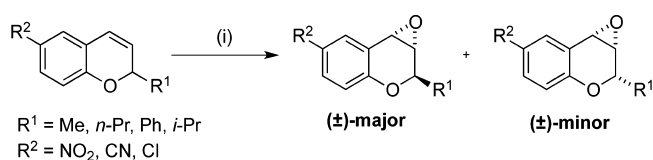


^aReagents and conditions: (i) (EtO)₂CH (1.2 equiv), NH₄NO₃ (0.25 equiv), ethanol (50 mL), 24 h, r.t.; (ii) phenol (2 equiv), 3-picoline (0.25 equiv), *p*-xylene (40 mL), 16 h, reflux.

Table 1. Synthesis of Racemic C6-Substituted Chromenes

	Compound	Yield (%)
	13a R = NO ₂	46
	13b R = CN	76
	13c R = Cl	43
	14a R = NO ₂	89
	14b R = CN	97
	14c R = Cl	74
	15a R = NO ₂	55
	15b R = CN	44
	15c R = Cl	13
	16a R = NO ₂	33
	16b R = CN	31
	16c R = Cl	16

Scheme 2^a



^aReagents and conditions: (i) *m*-CPBA, CH₂Cl₂, 1–8 h, 0 °C.

Asymmetric epoxidation of (±)-6-cyano-2-methyl-chromene **13b** under our standard nonaqueous conditions using catalyst **3** (Scheme 3) gave a promising initial result; a higher selectivity toward the product where the methyl group at C2 is *trans* to the epoxide moiety was observed compared to that observed when *m*-CPBA was used. At 52% conversion, chiral HPLC and ¹H NMR spectroscopic data of the mixture of inseparable

Table 2. Epoxidation of Racemic Chromenes Using *m*-CPBA

starting material	conversion (%)	epoxide	epoxide d.r.
13a	100	(±)-17a	2:1
13b	100	(±)-17b	1:1
14a	100	(±)-18a	2:1
14b	100	(±)-18b	3.5:1
15a	100	(±)-19a	<i>trans</i> only
15b	100	(±)-19b	<i>trans</i> only
16a	81	(±)-20a	4:1
16b	80	(±)-20b	4:1

diastereoisomers showed a 3:1 diastereoisomeric ratio, 86% ee for the major epoxide diastereoisomer **21**, 97% ee for the minor epoxide diastereoisomer **22**, and 37% ee for the unreacted starting material.

A number of chiral chromenes have previously been synthesized as single enantiomers.³⁵ On the basis of these reports and the optical rotation of our recovered chromene starting materials, we were able to assign the absolute configurations of the products obtained. The diastereofacial selectivity observed in the epoxidation of prochiral chromenes using catalyst **3** corresponds to the expected outcome based on our earlier work with this group of catalysts,^{17–19} providing further confirmation. Figure 3 indicates the preferred trajectory of oxidation of these substrate types when using iminium salt **3**. Encouraged by the results obtained for compound **13b**, we tested further chiral benzopyran substrates, allowing different electronic and steric influences to be investigated (Table 3).

In all cases, we again found that the compounds containing the chloro substituent on the aromatic ring were unstable to the epoxidation reaction conditions. The best results were obtained with compounds containing nitro and cyano substituents on the aromatic ring. In one case, chromene **13a**, the epoxidation reaction was run for a longer reaction time, reaching 84% conversion after 1 week. The diastereoisomeric ratio of the product epoxides was still 2.5:1, with a 70% ee observed for the major *trans* isomer and a 80% ee for the minor *cis* isomer. The remaining alkene was isolated with 64% ee. As expected, the observed k_{rel} values increase with the size of the 2-substituent in the alkene substrates.

To confirm unequivocally the absolute configuration of the major enantiomer obtained in these reactions, epoxide (+)-**19b** was reductively ring-opened by hydrogenolysis over a palladium on carbon catalyst to give alcohol **23**, containing the 2-substituted 3-hydroxybenzopyran core structure typical of the

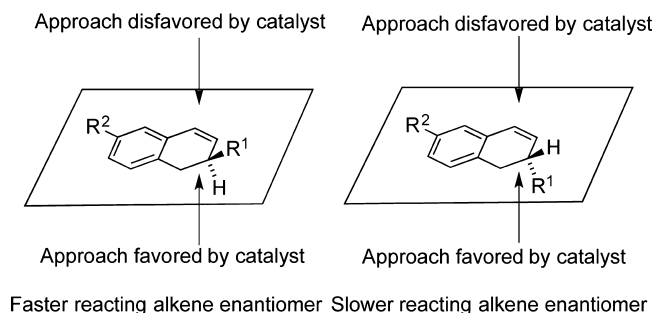


Figure 3. Directions of approach of active oxidant.

catechins, in quantitative yield. Alcohol **23** was then converted to the corresponding sulfonyl ester **24** by treatment with 10*S*-camphorsulfonyl chloride in 43% yield (Scheme 4).

Single-crystal X-ray analysis of **24** confirmed our assignment of absolute and relative configurations (see the Supporting Information).

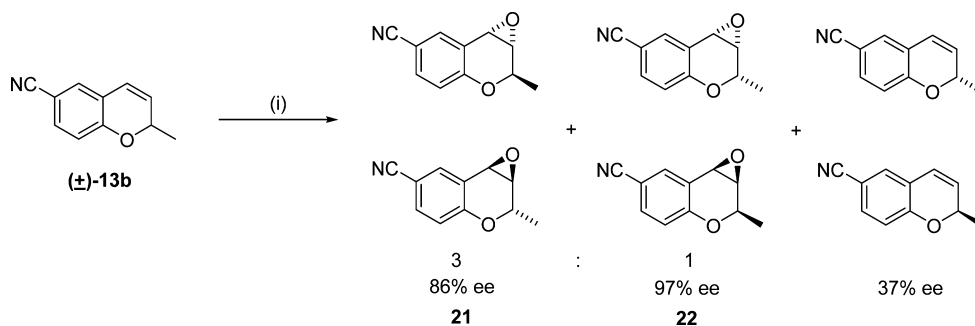
CONCLUSION

Kinetic resolution has been shown for the first time to be feasible in iminium salt-catalyzed asymmetric epoxidation. Enantioselectivities for epoxidation of racemic 2-substituted chromene substrates were good in all cases for the major epoxide diastereoisomer and were generally higher still for the minor diastereoisomer, with moderate enantioselectivity observed in the recovered starting material (15–50% ee). Increasing the size of the 2-substituent in the chromene substrates provided increases in diastereoselectivity and enantioselectivity, presumably due to steric effects.

EXPERIMENTAL SECTION

General Comments. HRMS measurements were conducted using APCI for the ionization method and an orbitrap mass analyzer. Enantiomeric excesses were determined by chiral high-performance liquid chromatography using a Chiralcel OD-H 5 μ m particle size column. All HPLC samples were run using hexane–isopropanol mixtures as eluent.

General Procedure for Acetal Formation.³⁷ The aldehyde was dissolved in the corresponding dried alcohol (molecular sieve) (100 mL). Ammonium nitrate (0.25 equiv) and triethylorthoformate (1.2 equiv) were added to the solution. The solution was stirred under a nitrogen atmosphere at room temperature for 24 h, and quenched with saturated aqueous sodium hydrogen carbonate (20 mL). The mixture was extracted using dichloromethane (4 \times 20 mL), the solution dried over magnesium sulfate, and the organic solvents were removed under

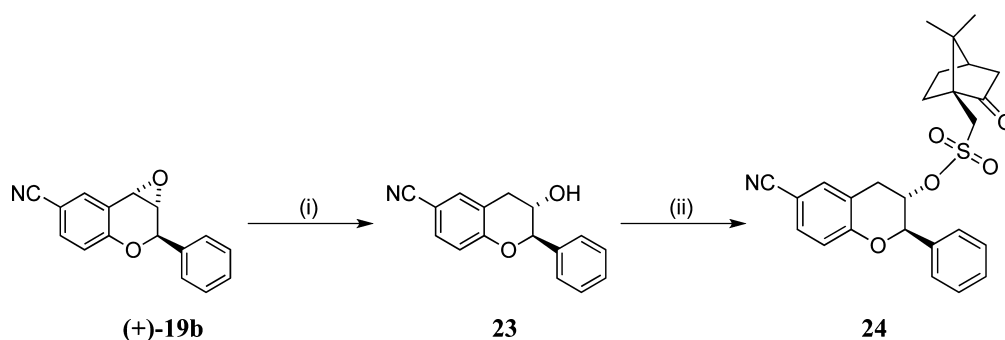
Scheme 3^a

^aReagents and conditions: (i) iminium salt **3** (10 mol %), TPPP (4 equiv), CHCl₃, –30 °C, 24 h. NB: the upper structures of each pair are the major enantiomers in each case

Table 3. Kinetic Resolution of Olefins Using Asymmetric Epoxidation Mediated Using Catalyst 3^a

starting material	conv. (%) ^b	epoxide	epoxide d.r. (trans:cis) ^d	major epoxide trans-diastereoisomer ee (%) ^c	minor epoxide cis-diastereoisomer ee (%) ^c	recovered chromene ee (%) ^c	k _{rel} ^e
13a	48	(-)-17a	2.5:1	87	97	26	2.3
13b	52	(-)-17b	3:1	86	97	37	2.9
14a	50	(-)-18a	4:1	87	98	40	3.4
14b	56	(-)-18b	3.5:1	73	92	41	2.8
15a	26	(+)-19a	trans only	76		17	3.4
15b	37	(+)-19b	trans only	74		14	1.9
16a	38	(-)-20a	10:1	76	82	42	8.0
16b	36	(-)-20b	16:1	88	99	50	27.9

^aAll reactions were carried out with substrate (1 equiv), catalyst (10 mol %), and tetraphenylphosphonium monoperoxydisulfate (TPPP) (4 equiv) in CHCl₃ at -30 °C. ^bConversion was determined from the ¹H NMR spectra of the crude reaction mixture. ^cEnantioselectivity was determined using chiral stationary phase HPLC with a Chiralcel OD-H column. ^dDiastereoisomeric ratios were determined from the ¹H NMR spectra of the reaction mixture after workup. ^ek_{rel} = ln[(1 - C)(1 - ee)]/ln[(1 - C)(1 + ee)], where C is the fraction of 13, 14, 15, or 16 consumed and ee is the percentage enantiomeric excess/100.^{21,22,36}

Scheme 4^a

^aReagents and conditions: (i) Pd/C, H₂ (1 atm), MeOH, r.t., 20 min, quantitative yield; (ii) (10S)-(+)-camphorsulfonyl chloride (1 equiv), Et₃N (2 equiv), PhMe, r.t., 24 h, 43%.

reduced pressure. The crude acetal was purified by vacuum distillation (35–45 °C, 2 mbar) to afford a pure colorless liquid product.

General Procedure for the Formation of Chromenes. The phenol (2 equiv) was dissolved in *p*-xylene, and 3-picoline (0.25 equiv) and the corresponding acetal (1 equiv) were added. The reaction mixture was heated under reflux under nitrogen for 24 h. The solvent was removed under reduced pressure. The product was purified by column chromatography using a petroleum ether/toluene mixture as eluent, yielding the chromene as a pure crystalline or oily product.

General Procedure for the Formation of Racemic Epoxides. The chromene and *meta*-chloroperbenzoic acid (1 equiv) were dissolved in dichloromethane (5 mL) at 0 °C, and stirred until the reaction reached completion. Saturated aqueous sodium hydrogen carbonate (2 mL) was added. The organic layer was extracted with water and brine, and the aqueous washings were extracted with further dichloromethane. The combined organic extracts were dried over magnesium sulfate, and solvents were removed under reduced pressure. The crude product was purified by column chromatography using an ethyl acetate/petroleum ether/triethylamine mixture as eluent.

General Procedure for the Formation of Chiral Epoxides. Tetraphenylphosphonium monoperoxydisulfate (4 equiv) and iminium salt (10 mol %) were dissolved in chloroform (20 mL per 0.1 g of chromene) and cooled to -30 °C. The required chromene (1 equiv) dissolved in chloroform (2 mL per 0.1 g of chromene) was then added slowly over 10 min to the reaction mixture. The reaction progress was monitored by ¹H NMR spectroscopy of the crude reaction mixture. At 50% conversion, the reactions were quenched by the addition of diethyl ether (20 mL per 0.1 g of chromene). The catalyst was removed using filtration through Celite and washed with diethyl ether (10 mL per 0.1 g of chromene), and the combined organic solvents were removed under reduced pressure. The crude product was purified

by column chromatography using an ethyl acetate/petroleum ether/triethylamine mixture as eluent.

1,1-Diethoxybut-2-ene 9.^{37–39} 1,1-Diethoxybut-2-ene was prepared using the general procedure for acetal formation from crotonaldehyde (10 g, 143 mmol), yielding the desired compound 9 as a colorless liquid (10.6 g, 51%) after purification by vacuum distillation (2 mbar, 35–38 °C). ¹H NMR (300 MHz, CDCl₃): δ_H 1.17 (6H, t, *J* = 7 Hz), 1.65 (3H, dd, *J* = 7, 2 Hz), 3.38–3.45 (2H, m), 3.50–3.61 (2H, m), 4.77 (1H, d, *J* = 6 Hz), 5.48 (1H, ddq, *J* = 16, 6, 2 Hz), 5.78 (1H, ddq, *J* = 16, 7, 1 Hz). ¹³C NMR (75 MHz, CDCl₃): δ_C 14.9, 17.2, 60.7, 101.7, 128.9, 129.5.

(3,3-Diethoxyprop-1-enyl)benzene 10.^{40,41} (3,3-Diethoxyprop-1-enyl)benzene was prepared using the general procedure for acetal formation from *trans*-cinnamaldehyde (12 g, 91 mmol), yielding the desired compound 10 as a colorless liquid (15.6 g, 83%) after purification by vacuum distillation (2 mbar, 37–40 °C). ¹H NMR (300 MHz, CDCl₃): δ_H 1.25 (6H, t, *J* = 7 Hz), 3.40–3.83 (4H, m), 5.06 (1H, dd, *J* = 5, 1 Hz), 6.21 (1H, dd, *J* = 16, 5 Hz), 6.71 (1H, d, *J* = 16 Hz), 7.08–7.47 (5H, m). ¹³C NMR (75 MHz, CDCl₃): δ_C 15.1, 60.9, 101.5, 126.76, 126.83, 128.0, 128.6, 132.93, 136.3.

1,1-Diethoxyhex-2-ene 11.⁴² 1,1-Diethoxyhex-2-ene was prepared using the general procedure for acetal formation from hex-2-enal (3 g, 30.6 mmol), yielding compound 11 as a colorless liquid (2.1 g, 40%) after purification by vacuum distillation (2 mbar, 35–37 °C). ¹H NMR (300 MHz, CDCl₃): δ_H 0.79 (3H, t, *J* = 7.35 Hz), 1.09 (6H, t, *J* = 7.05 Hz), 1.24–1.37 (2H, m), 1.93 (2H, dd, *J* = 8, 15 Hz), 3.31–3.51 (4H, m), 4.71 (1H, d, *J* = 6 Hz), 5.37 (1H, dd, *J* = 6, 16 Hz), 5.68 (1H, dt, *J* = 7, 16 Hz). ¹³C NMR (75 MHz, CDCl₃): δ_C 13.3, 14.9, 21.7, 33.9, 60.6, 101.7, 127.5, 134.6.

1,1-Diethoxy-4-methylpent-2-ene 12.⁴³ 1,1-Diethoxy-4-methylpent-2-ene was prepared from 4-methyl-2-pentenal (2.0 g, 20.4 mmol), using the general procedure for acetal formation, yielding the desired compound 12 as a pale yellow liquid (2.75 g, 78%) after

purification by vacuum distillation (2 mbar, 42–45 °C). ^1H NMR (300 MHz, CDCl_3): δ_{H} 0.88 (6H, d, $J = 7$ Hz), 1.08 (6H, t, $J = 6$ Hz), 2.10–2.28 (1H, m), 3.23–3.41 (2H, m), 3.40–3.55 (2H, m), 4.69 (1H, d, $J = 6$ Hz), 5.30 (1H, dd, $J = 16, 6$ Hz), 5.65 (1H, dd, $J = 16, 6$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 14.5, 21.4, 30.0, 60.0, 101.3, 124.3, 140.8.

6-Nitro-2-methyl-chromene 13a.²⁵ Compound (13a) was prepared using the general procedure for chromene formation from 4-nitrophenol (3.19 g, 23.0 mmol) and 1,1-diethoxybut-2-ene **9** (1.65 g, 11.49 mmol), yielding compound (13a) as a yellow crystalline solid (1.01 g, 46%; mp = 67–69 °C, lit.²⁵ 66–66.5 °C) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. ν_{max} (film)/ cm^{-1} : 1575, 1506, 1480, 1373, 911. ^1H NMR (300 MHz, CDCl_3): δ_{H} 1.49 (3H, d, $J = 7$ Hz), 5.14–5.22 (1H, m), 5.80 (1H, dd, $J = 10, 3$ Hz), 6.41 (1H, dd, $J = 10, 2$ Hz), 6.81 (1H, d, $J = 9$ Hz), 7.87 (1H, d, $J = 3$ Hz), 8.02 (1H, dd, $J = 9, 3$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 22.0, 73.2, 116.4, 121.4, 122.3, 125.5, 128.7, 159.2. HRMS m/z : 191.0578 [M^+]; $\text{C}_{10}\text{H}_9\text{NO}_3$ requires 191.0577. HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 5.7 min (48.76%), 5.97 min (51.24%).

6-Cyano-2-methyl-chromene 13b.²⁵ Compound (13b) was prepared using the general procedure for chromene formation from 4-cyanophenol (1.65 g, 13.9 mmol) and 1,1-diethoxybut-2-ene **9** (1.0 g, 6.93 mmol), yielding compound (13b) as a cream solid (0.90 g, 76%; mp = 53–55 °C, lit.²⁵ 55.5–56 °C) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. ν_{max} (film)/ cm^{-1} : 2360, 2342, 2225, 1605, 1488, 1373, 1253, 765. ^1H NMR (400 MHz, CDCl_3): δ_{H} 1.46 (3H, d, $J = 7$ Hz), 5.08–5.14 (1H, m), 5.75 (1H, dd, $J = 10, 3$ Hz), 6.33 (1H, dd, $J = 10, 2$ Hz), 6.79 (1H, d, $J = 8$ Hz), 7.22 (1H, d, $J = 2$ Hz), 7.38 (1H, dd, $J = 8, 2$ Hz). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 21.9, 72.7, 104.2, 117.1, 119.4, 122.1, 122.3, 128.6, 130.4, 133.6, 157.3. HRMS m/z : 171.0678 [M^+]; $\text{C}_{11}\text{H}_9\text{NO}$ requires 171.0679. HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 5.93 min (49.45%), 6.41 min (50.55%).

6-Chloro-2-methyl-chromene 13c.²⁵ Compound (13c) was prepared using the general procedure for chromene formation from 4-chlorophenol (2.95 g, 23.04 mmol) and 1,1-diethoxybut-2-ene **9** (1.66 g, 11.52 mmol), yielding compound (13c) as a yellow liquid (0.892 g, 43%) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. ν_{max} (film)/ cm^{-1} : 3050, 2977, 2932, 1767, 1645, 1481, 1368, 1208. ^1H NMR (300 MHz, CDCl_3): δ_{H} 1.44 (3H, d, $J = 7$ Hz), 4.95–5.03 (1H, m), 5.70 (1H, dd, $J = 10, 3$ Hz), 6.31 (1H, dd, $J = 10, 2$ Hz), 6.71 (1H, d, $J = 9$ Hz), 6.94 (1H, d, $J = 3$ Hz), 7.05 (1H, dd, $J = 9, 3$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 21.4, 71.8, 117.5, 123.0, 123.3, 125.8, 126.2, 128.4, 128.8, 152.2. HRMS m/z : 180.0338 [M^+]; $\text{C}_{10}\text{H}_9\text{ClO}$ requires 180.0342. HPLC trace (98:2 hexane/isopropanol, 0.5 mL/min); inseparable: 10.20 min (100%).

6-Nitro-2-propyl-chromene 14a. Compound (14a) was prepared using the general procedure for chromene formation from 4-nitrophenol (1.0 g, 7.18 mmol) and 1,1-diethoxyhex-2-ene **11** (0.62 g, 3.59 mmol), yielding compound (14a) as a viscous orange liquid (0.7 g, 89%) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. ν_{max} (film)/ cm^{-1} : 2961, 1614, 1580, 1515, 1483, 1342, 1242, 1091, 1002, 747. ^1H NMR (400 MHz, CDCl_3): δ_{H} 0.96 (3H, t, $J = 7$ Hz), 1.40–1.85 (4H, m), 4.99–5.11 (1H, m), 5.79 (1H, dd, $J = 10, 3$ Hz), 6.40 (1H, dd, $J = 10, 3$ Hz), 6.79 (1H, d, $J = 9$ Hz), 7.84 (1H, d, $J = 3$ Hz), 8.00 (1H, dd, $J = 9, 3$ Hz). ^{13}C NMR (100 MHz, CDCl_3): 13.7, 17.7, 37.9, 76.5, 116.1, 121.5, 122.1, 123.3, 125.3, 127.6, 141.6, 159.3. HRMS m/z : 220.0962 [$\text{M} + \text{H}$] $^+$; [$\text{C}_{12}\text{H}_{13}\text{NO}_3 + \text{H}$] $^+$ requires 220.0968. HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 4.89 min (49.49%), 5.18 min (50.51%).

6-Cyano-2-propyl-chromene 14b. Compound (14b) was prepared using the general procedure for chromene formation from 4-cyanophenol (1.73 g, 14.5 mmol) and 1,1-diethoxyhex-2-ene **11** (1.25 g, 7.25 mmol), yielding compound (14b) as a straw-yellow colored liquid (1.40 g, 97%) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. ν_{max} (film)/ cm^{-1} : 2960, 2874, 2225, 1605, 1489, 1381, 1253,

1130, 1005. ^1H NMR (300 MHz, CDCl_3): δ_{H} 0.94 (3H, t, $J = 7$ Hz), 1.40–1.84 (4H, m), 4.91–5.04 (1H, m), 5.74 (1H, dd, $J = 10, 3$ Hz), 6.33 (1H, dd, $J = 10, 2$ Hz), 6.77 (1H, d, $J = 8$ Hz), 7.19 (1H, d, $J = 2$ Hz), 7.35 (1H, dd, $J = 8, 2$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 13.7, 17.7, 37.8, 76.0, 103.9, 116.8, 119.2, 122.2, 122.4, 127.5, 130.1, 133.4, 157.4. HRMS m/z : 200.1065 [$\text{M} + \text{H}$] $^+$; [$\text{C}_{13}\text{H}_{13}\text{NO} + \text{H}$] $^+$ requires 200.1070. HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 5.11 min (50.47%), 5.47 min (49.53%).

6-Chloro-2-propyl-chromene 14c. Compound (14c) was prepared using the general procedure for chromene formation from 4-chlorophenol (1.50 g, 11.7 mmol) and 1,1-diethoxyhex-2-ene **11** (1.0 g, 5.85 mmol), yielding compound (14c) as a yellow liquid (0.9 g, 74%) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. ν_{max} (film)/ cm^{-1} : 2960, 2873, 1481, 1378, 1235, 1010, 878. ^1H NMR (300 MHz, CDCl_3): δ_{H} 0.95 (3H, t, $J = 7$ Hz), 1.42–1.82 (4H, m), 4.80–4.89 (1H, m), 5.72 (1H, dd, $J = 10, 3$ Hz), 6.32 (1H, dd, $J = 10, 2$ Hz), 6.70 (1H, d, $J = 9$ Hz), 6.93 (1H, d, $J = 3$ Hz), 7.03 (1H, dd, $J = 9, 3$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 13.8, 17.9, 37.3, 75.1, 117.2, 123.0, 123.3, 125.5, 126.0, 127.3, 128.6, 152.1. HRMS m/z : 209.0722 [$\text{M} + \text{H}$] $^+$; [$\text{C}_{12}\text{H}_{13}\text{ClO} + \text{H}$] $^+$ requires 209.0728. HPLC trace (99:1 hexane/isopropanol, 30 min, 0.5 mL/min); 7.61 min (56.49%), 7.90 min (43.51%).

6-Nitro-2-phenyl-chromene 15a.²⁵ Compound (15a) was prepared using the general procedure for chromene formation from 4-nitrophenol (1.0 g, 7.2 mmol) and (3,3-diethoxyprop-1-enyl)benzene **10** (0.73 g, 3.56 mmol), yielding compound (15a) as a cream solid (0.5 g, 55%; mp = 104–106 °C) after purification by column chromatography using a petroleum ether/toluene (3:2) mixture as eluent. ν_{max} (film)/ cm^{-1} : 3063, 3034, 1647, 1612, 1576, 1480, 1343, 1261, 913. ^1H NMR (300 MHz, CDCl_3): δ_{H} 5.94 (1H, dd, $J = 10, 3$ Hz), 6.07 (1H, dd, $J = 3, 2$ Hz), 6.59 (1H, dd, $J = 10, 2$ Hz), 6.81 (1H, d, $J = 9$ Hz), 7.35–7.46 (5H, m), 7.93 (1H, d, $J = 3$ Hz), 8.01 (1H, dd, $J = 9, 3$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 78.5, 116.3, 120.9, 122.3, 122.4, 125.6, 127.2, 129.0, 129.1, 139.5, 141.8, 158.6. m/z : 254.0799 [$\text{M} + \text{H}$] $^+$; [$\text{C}_{15}\text{H}_{11}\text{NO}_3 + \text{H}$] $^+$ requires 254.0812. HPLC trace (95:5 hexane/isopropanol, 0.5 mL/min); 23.55 min (49.20%), 24.66 min (50.80%).

6-Cyano-2-phenyl-chromene 15b.⁴⁴ Compound (15b) was prepared using the general procedure for chromene formation from 4-cyanophenol (1.0 g, 8.4 mmol) and (3,3-diethoxyprop-1-enyl)benzene **10** (0.86 g, 4.16 mmol), yielding compound (15b) as a white crystalline powder (0.43 g, 44%; mp = 123–125 °C) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. ν_{max} (film)/ cm^{-1} : 3033, 2222, 1677, 1602, 1570, 1489, 1374, 1251, 1229, 1128, 893, 825. ^1H NMR (300 MHz, CDCl_3): δ_{H} 5.90 (1H, dd, $J = 10, 3$ Hz), 6.02 (1H, dd, $J = 3, 2$ Hz), 6.52 (1H, dd, $J = 10, 2$ Hz), 6.80 (1H, d, $J = 8$ Hz), 7.29 (1H, d, $J = 2$ Hz), 7.35–7.45 (6H, m). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 78.0, 104.4, 117.0, 119.1, 121.7, 122.2, 126.3, 127.1, 128.9, 129.0, 130.4, 133.8, 139.7, 156.8. m/z : 251.1180 [$\text{M} + \text{NH}_4$] $^+$; [$\text{C}_{16}\text{H}_{11}\text{NO} + \text{NH}_4$] $^+$ requires 251.1179. HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min, 230 nm); 41.34 min (47.94%), 43.47 min (52.06%).

6-Chloro-2-phenyl-chromene 15c.²⁵ Compound (15c) was prepared using the general procedure for chromene formation from 4-chlorophenol (1.0 g, 7.62 mmol) and (3,3-diethoxyprop-1-enyl)benzene **10** (0.78 g, 3.81 mmol), yielding compound (15c) as a viscous colorless liquid (0.12 g, 13%) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. ν_{max} (film)/ cm^{-1} : 3032, 1639, 1477, 1424, 1368, 1261, 1231, 1200, 1121, 1034, 814, 755, 697. ^1H NMR (300 MHz, CDCl_3): δ_{H} 5.88 (1H, dd, $J = 10, 3$ Hz), 5.94 (1H, dd, $J = 3, 2$ Hz), 6.47 (1H, dd, $J = 10, 2$ Hz), 6.72 (1H, d, $J = 9$ Hz), 7.02 (1H, d, $J = 3$ Hz), 7.08 (1H, dd, $J = 9, 3$ Hz), 7.37–7.49 (5H, m). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 77.4, 117.5, 122.8, 123.3, 126.0, 126.2, 126.3, 127.2, 128.8, 128.9, 129.2, 140.4, 151.8. m/z : 243.0561 [$\text{M} + \text{H}$] $^+$; [$\text{C}_{15}\text{H}_{11}\text{ClO} + \text{H}$] $^+$ requires 243.0571. HPLC trace (99.9:0.1 hexane/isopropanol, 0.25 mL/min); inseparable: 104.77 min (100%).

6-Nitro-2-isopropyl-chromene 16a. Compound (16a) was prepared using the general procedure for chromene formation from 4-nitrophenol (0.80 g, 5.54 mmol) and 1,1-diethoxy-4-methylpent-2-

ene **12** (0.48 g, 2.77 mmol), yielding compound (**16a**) as a pale yellow viscous oil (0.2 g, 33%) after purification by column chromatography using a petroleum ether/toluene (3:2) mixture as eluent. ν_{\max} (film)/ cm^{-1} : 3073, 2965, 2874, 1613, 1579, 1335, 1241, 1089. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 1.00 (6H, dd, $J = 8, 7$ Hz), 1.95–2.03 (1H, m), 4.82–4.84 (1H, m), 5.77 (1H, dd, $J = 10, 3$ Hz), 6.43 (1H, dd, $J = 10, 2$ Hz), 6.77 (1H, d, $J = 9$ Hz), 7.81 (1H, d, $J = 3$ Hz), 7.97 (1H, dd, $J = 9, 3$ Hz). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ_{C} 17.1, 17.6, 34.2, 81.6, 115.9, 121.5, 122.2, 123.1, 125.5, 126.1, 141.5, 160.0. m/z : 237.1229 [$\text{M} + \text{NH}_4$] $^+$; [$\text{C}_{12}\text{H}_{13}\text{NO}_3 + \text{NH}_4$] $^+$ requires 237.1234. HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 4.84 min (48.91%), 5.12 min (51.09%).

6-Cyano-2-isopropyl-chromene 16b. Compound (**16b**) was prepared using the general procedure for chromene formation from 4-cyanophenol (0.97 g, 8.1 mmol) and 1,1-diethoxy-4-methylpent-2-ene **12** (0.7 g, 4.05 mmol), yielding compound (**16b**) as a colorless viscous oil (0.25 g, 31%) after purification by column chromatography using a petroleum ether/toluene (3:2) mixture as eluent. ν_{\max} (film)/ cm^{-1} : 3053, 2965, 2931, 2874, 2225, 1603, 1489, 1379, 1252, 1130. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ_{H} 0.97 (6H, dd, $J = 7, 5$ Hz), 1.90–2.01 (1H, m), 4.74–4.77 (1H, m), 5.72 (1H, dd, $J = 10, 3$ Hz), 6.35 (1H, dd, $J = 10, 2$ Hz), 6.75 (1H, d, $J = 8$ Hz), 7.16 (1H, d, $J = 2$ Hz), 7.32 (1H, dd, $J = 8, 2$ Hz). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ_{C} 17.1, 17.5, 33.9, 81.0, 103.7, 116.5, 119.3, 122.3, 122.9, 125.9, 130.2, 133.5, 158.0. m/z : 200.1062 [$\text{M} + \text{H}$] $^+$; [$\text{C}_{13}\text{H}_{13}\text{NO} + \text{H}$] $^+$ requires 200.1070. HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 5.02 min (49.90%), 5.42 min (50.10%).

6-Chloro-2-isopropyl-chromene 16c. Compound (**16c**) was prepared using the general procedure for chromene formation from 4-chlorophenol (1.59 g, 12.4 mmol) and 1,1-diethoxy-4-methylpent-2-ene **12** (1.06 g, 6.2 mmol), yielding compound (**16c**) as a colorless oil (0.21 g, 16%) after purification by column chromatography using a petroleum ether/toluene (3:2) mixture as eluent. ν_{\max} (film)/ cm^{-1} : 3050, 2963, 2931, 2873, 1637, 1481, 1234, 1203, 1123, 1019, 997, 878, 814, 698. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ_{H} 1.00 (6H, dd, $J = 7, 1$ Hz), 1.93–2.04 (1H, m), 4.61–4.65 (1H, m), 5.73 (1H, dd, $J = 10, 3$ Hz), 6.36 (1H, dd, $J = 10, 2$ Hz), 6.70 (1H, d, $J = 9$), 6.92 (1H, d, $J = 3$ Hz), 7.03 (1H, dd, $J = 9, 3$ Hz). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ_{C} 17.5, 17.6, 33.4, 80.2, 116.9, 123.3, 123.6, 125.3, 125.6, 126.0, 128.7, 152.7. HPLC trace (99.9:0.1 hexane/isopropanol, 0.25 mL/min); 14.80 min (49.74%), 15.87 min (50.26%).

6-Nitro-2-methyl-chromene Oxide 17a. Using General Procedure A. 6-Nitro-2-methyl-chromene **13a** (0.205 g, 1.07 mmol) and *meta*-chloroperbenzoic acid (0.184 g, 1.07 mmol) were dissolved in dichloromethane (40 mL) at 0 °C, and left to stir for 8 h. The racemic epoxide was isolated as a cream solid (0.20 g, 90%; mp = 86–88 °C) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (3:1:0.1) mixture as eluent. ν_{\max} (film)/ cm^{-1} : 3075, 2984, 2935, 1620, 1591, 1521, 1487, 1341, 1257, 1094, 878, 746. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ_{H} 1.36 (3H, d, $J = 7$ Hz, *trans*), 1.61 (3H, d, $J = 7$ Hz, *cis*), 3.66 (1H, dd, $J = 4, 1$ Hz, *trans*), 3.73 (1H, d, $J = 4$ Hz, *cis*), 3.95 (1H, d, $J = 4$ Hz, *trans*), 4.00 (1H, d, $J = 4$ Hz, *cis*), 4.43 (1H, q, $J = 7$ Hz, *cis*), 4.87 (1H, q, $J = 7$ Hz, *trans*), 6.90 (2H, d, $J = 9$ Hz, *cis* and *trans*), 8.14 (2H, dd, $J = 9, 3$ Hz, *cis* and *trans*), 8.28 (1H, d, $J = 3$ Hz, *trans*), 8.31 (1H, d, $J = 3$ Hz, *cis*), (ratio of *trans*:*cis*, 2:1). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ_{C} 16.6, 18.3, 48.1, 49.5, 58.6, 58.8, 69.7, 69.9, 117.9, 118.6, 120.3, 120.6, 125.9, 126.0, 126.2, 126.4, 141.5, 141.6, 157.6, 159.4. HRMS m/z : 206.0461 [$\text{M} - \text{H}$] $^-$; [$\text{C}_{10}\text{H}_9\text{NO}_4 - \text{H}$] $^-$ requires 206.0459. HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 60.31 min (21.22%), 74.09 min (21.79%), 95.06 min (28.69%), 100.87 min (28.29%).

Using General Procedure B. Tetraphenylphosphonium monoperoxysulfate (1.71 g, 3.8 mmol) and iminium salt **3** (0.068 g, 0.095 mmol) were dissolved in chloroform (40 mL) and cooled to –30 °C. 6-Nitro-2-methyl-chromene **13a** (0.182 g, 0.95 mmol) dissolved in chloroform (4 mL) was then added slowly over 10 min to the reaction mixture. The reaction was quenched at 48% conversion, and enantioenriched 6-nitro-2-methylchromene epoxide was isolated as a cream solid (0.065 g, 33%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (3:1:0.1)

mixture as eluent. $[\alpha_{\text{D}}] = -58.4^\circ$, (c 0.005 g/mL CH_2Cl_2). HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 58.29 min (0.40%) *cis*, 70.71 min (26.78%) *cis*, 91.36 min (68.02%) *trans*, 97.75 min (4.79%) *trans*.

6-Cyano-2-methyl-chromene Epoxide 17b. Using General Procedure A. 6-Cyano-2-methyl-chromene **13b** (1.10 g, 6.42 mmol) and *meta*-chloroperbenzoic acid (1.10 g, 6.42 mmol) were dissolved in dichloromethane (100 mL) at 0 °C, and left to react for 6 h. The racemic epoxide was isolated as a cream solid (1.02 g, 85%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (3:1:0.1) mixture as eluent. ν_{\max} (film)/ cm^{-1} : 2917, 2849, 2227, 1615, 1581, 1495, 1253, 1229, 1159, 873. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ_{H} 1.33 (3H, d, $J = 7$ Hz, *trans*), 1.58 (3H, d, $J = 7$ Hz, *cis*), 3.63 (1H, dd, $J = 4, 1$ Hz, *trans*), 3.69 (1H, dd, $J = 4, 1$ Hz, *cis*), 3.87 (1H, d, $J = 4$ Hz, *trans*), 3.92 (1H, d, $J = 4$ Hz, *cis*), 4.37 (1H, q, $J = 6$ Hz, *cis*), 4.82 (1H, q, $J = 6$ Hz, *trans*), 6.88 (2H, d, $J = 9$ Hz, *cis* and *trans*), 7.52 (2H, dd, $J = 9, 2$ Hz, *cis* and *trans*), 7.64 (1H, d, $J = 2$ Hz, *trans*), 7.66 (1H, d, $J = 2$ Hz, *cis*). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ_{C} 16.5, 18.4, 48.0, 49.4, 58.8, 59.1, 69.3, 69.5, 104.4, 104.5, 118.4, 118.7, 119.2, 121.1, 121.4, 133.9, 134.1, 134.3, 134.5, 155.7, 157.7. HRMS m/z : 187.0628 [M^+]; $\text{C}_{11}\text{H}_9\text{NO}_2$ requires 187.0633. HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 76.82 min (22.87%), 119.490 min (27.75%), 127.70 min (23.05%), 137.62 min (26.33%).

Using General Procedure B. Tetraphenylphosphonium monoperoxysulfate (0.9 g, 2 mmol) and iminium salt **3** (0.036 g, 0.05 mmol) were dissolved in chloroform (20 mL) and cooled to –30 °C. 6-Cyano-2-methyl-chromene **13b** (0.085 g, 0.50 mmol) dissolved in chloroform (2 mL) was then added slowly over 10 min to the reaction mixture. The reaction was quenched at 52% conversion, and enantioenriched 6-cyano-2-methylchromene epoxide was isolated as a cream solid (0.031 g, 33%; mp = 77–79 °C) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (3:1:0.1) mixture as eluent. $[\alpha_{\text{D}}] = -74^\circ$, (c 0.01 g/mL CHCl_3). HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 74.88 min (0.50%) *cis*, 116.04 min (5.14%) *trans*, 125.01 min (28.11%) *cis*, 132.81 min (66.26%) *trans*.

6-Nitro-2-propyl-chromene Epoxide 18a. Using General Procedure A. 6-Nitro-2-propyl-chromene **14a** (0.310 g, 1.43 mmol) and *meta*-chloroperbenzoic acid (0.245 g, 1.43 mmol) were dissolved in dichloromethane (50 mL) at 0 °C, and left to stir for 5 h. The racemic epoxide was isolated as a yellow oil (0.265 g, 79%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (10:1:0.1) mixture as eluent. ν_{\max} (film)/ cm^{-1} : 2961, 2874, 1619, 1591, 1516, 1486, 1340, 1244, 1088. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 0.96 (3H, t, $J = 7$ Hz, *trans*), 1.04 (3H, t, $J = 7$ Hz, *cis*), 1.45–2.02 (8H, m, *cis* and *trans*), 3.67 (1H, dd, $J = 4, 1$ Hz, *trans*), 3.76 (1H, dd, $J = 4, 1$ Hz, *cis*), 3.94 (1H, d, $J = 4$ Hz, *trans*), 3.99 (1H, d, $J = 4$ Hz, *cis*), 4.26–4.30 (1H, m, *cis*), 4.70–4.73 (1H, m, *trans*), 6.91 (1H, d, $J = 9$ Hz, *trans*), 6.92 (1H, d, $J = 9$ Hz, *cis*), 8.14 (1H, dd, $J = 9, 3$ Hz, *cis*), 8.15 (1H, dd, $J = 9, 3$ Hz, *trans*), 8.28 (1H, d, $J = 3$ Hz, *trans*), 8.31 (1H, d, $J = 3$ Hz, *cis*), (ratio of *trans*:*cis*, 2:1). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 14.0, 14.1, 18.4, 19.0, 33.3, 35.1, 48.6, 49.4, 58.4, 73.3, 73.6, 118.1, 118.7, 120.7, 121.1, 126.1, 126.2, 126.3, 126.6, 141.6, 141.7, 157.9, 159.6. HRMS m/z : 236.0911 [$\text{M} + \text{H}$] $^+$; [$\text{C}_{12}\text{H}_{13}\text{NO}_4 + \text{H}$] $^+$ requires 236.0918. HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 41.77 min (13.78%), 51.76 min (13.55%), 59.50 min (39.42%), 65.630 min (33.25%).

Using General Procedure B. Tetraphenylphosphonium monoperoxysulfate (2.31 g, 5.12 mmol) and iminium salt **3** (0.092 g, 0.128 mmol) were dissolved in chloroform (60 mL) and cooled to –30 °C. 6-Nitro-2-propyl-chromene **14a** (0.28 g, 1.28 mmol) dissolved in chloroform (6 mL) was then added slowly over 10 min to the reaction mixture. The reaction was quenched at 50% conversion, and enantioenriched 6-nitro-2-propyl-chromene epoxide was isolated as a yellow oil (0.12 g, 40%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (10:1:0.1) mixture as eluent. $[\alpha_{\text{D}}] = -35^\circ$, (c 0.01 g/mL CHCl_3). HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 40.45 min (0.37%), 49.52 min (17.40%), 57.23 min (72.28%), 61.39 min (9.96%).

6-Cyano-2-propyl-chromene Epoxide 18b. *Using General Procedure A.* 6-Cyano-2-propyl-chromene **14b** (0.150 g, 0.75 mmol) and *meta*-chloroperbenzoic acid (0.130 g, 0.75 mmol) were dissolved in dichloromethane (25 mL) at 0 °C, and left to stir for 5 h. The racemic epoxide was isolated as a colorless oil (0.13 g, 81%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (5:1:0.1) mixture as eluent. ν_{\max} (film)/cm⁻¹: 2963, 2925, 2224, 1745, 1610, 1579, 1494, 1247, 1170. ¹H NMR (400 MHz, CDCl₃): δ_{H} 0.96 (3H, t, *J* = 7 Hz, *trans*), 1.03 (3H, t, *J* = 7 Hz, *cis*), 1.45–1.85 (8H, m, *cis* and *trans*), 3.65 (1H, dd, *J* = 4, 1 Hz, *trans*), 3.74 (1H, d, *J* = 4 Hz, *cis*), 3.87 (1H, d, *J* = 4 Hz, *trans*), 3.91 (1H, d, *J* = 4 Hz, *cis*), 4.20–4.23 (1H, m, *cis*), 4.66–4.69 (1H, m, *trans*), 6.89 (1H, d, *J* = 9 Hz, *trans*), 6.90 (1H, d, *J* = 9 Hz, *cis*), 7.52–7.55 (2H, m, *cis* and *trans*), 7.64 (1H, d, *J* = 2 Hz, *trans*), 7.67 (1H, d, *J* = 2 Hz, *cis*) (ratio of *trans*:*cis*, 3.5:1). ¹³C NMR (75 MHz, CDCl₃): δ_{C} : 13.6, 13.8, 18.1, 18.6, 32.9, 34.9, 48.1, 49.0, 58.3, 72.7, 73.0, 104.5, 118.4, 118.7, 119.1, 121.7, 133.9, 134.0, 134.3, 134.6, 156.0. HRMS *m/z*: 238.0840 [M + Na]⁺; [C₁₃H₁₃NO₂ + Na]⁺ requires 238.0838. HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 27.14 min (10.86%), 36.32 min (38.48%), 38.24 min (10.67%), 39.82 min (39.99%).

Using General Procedure B. Tetraphenylphosphonium monoperoxysulfate (2.15 g, 4.76 mmol) and iminium salt **3** (0.086 g, 0.12 mmol) were dissolved in chloroform (50 mL) and cooled to –30 °C. 6-Cyano-2-propyl-chromene **14b** (0.24 g, 1.19 mmol) dissolved in chloroform (5 mL) was then added slowly over 10 min to the reaction mixture. The reaction was quenched at 56% conversion, and enantioenriched 6-cyano-2-propyl-chromene epoxide was isolated as a colorless oil (0.1 g, 39%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (5:1:0.1) mixture as eluent. [α_{D}] = –22°, (*c* 0.004 g/mL, CH₂Cl₂). HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 27.10 min (0.93%), 36.17 min (10.56%), 37.63 min (21.42%), 39.38 min (67.09%).

6-Nitro-2-phenyl-chromene Epoxide 19a. *Using General Procedure A.* 6-Nitro-2-phenyl-chromene **15a** (0.22 g, 0.87 mmol) and *meta*-chloroperbenzoic acid (0.15 g, 0.87 mmol) were dissolved in dichloromethane (40 mL) at 0 °C, and left to stir for 8 h. The racemic epoxide was isolated as a colorless solid (0.22 g, 94%; mp = 120–122 °C) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (4:1:0.1) mixture as eluent. ν_{\max} (film)/cm: 3071, 2928, 1620, 1591, 1515, 1485, 1339, 1236, 1041. ¹H NMR (300 MHz, CDCl₃): δ_{H} 3.94 (1H, dd, *J* = 4, 1 Hz), 4.13 (1H, d, *J* = 4 Hz), 5.73 (1H, s), 6.92 (1H, d, *J* = 9 Hz), 7.27–7.38 (5H, m), 8.17 (1H, dd, *J* = 9, 3 Hz), 8.36 (1H, d, *J* = 3 Hz) (*only trans* observed). ¹³C NMR (75 MHz, CDCl₃): δ_{C} : 48.8, 58.1, 75.7, 100.4, 118.6, 120.7, 126.2, 126.9, 127.2, 129.4, 129.6, 136.3, 158.1. HRMS *m/z*: 287.1025 [M + NH₄]⁺; [C₁₅H₁₁NO₄ + NH₄]⁺ requires 287.1026. HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 26.63 min (48.44%), 43.18 min (51.56%).

Using General Procedure B. Tetraphenylphosphonium monoperoxysulfate (3.36 g, 7.44 mmol) and iminium salt **3** (0.132 g, 0.186 mmol) were dissolved in chloroform (100 mL) and cooled to –30 °C. 6-Nitro-2-phenyl-chromene **15a** (0.47 g, 1.86 mmol) dissolved in chloroform (10 mL) was then added slowly over 10 min to the reaction mixture. The reaction was quenched at 26% conversion, and enantioenriched 6-nitro-2-phenyl-chromene epoxide was isolated as a colorless solid (0.075 g, 15%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (4:1:0.1) mixture as eluent. [α_{D}] = +51°, (*c* 0.01 g/mL, CH₂Cl₂); HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 23.97 min (88.13%), 37.01 min (11.87%).

6-Cyano-2-phenyl-chromene Epoxide 19b. *Using General Procedure A.* 6-Cyano-2-phenyl-chromene **15b** (0.165 g, 0.71 mmol) and *meta*-chloroperbenzoic acid (0.12 g, 0.71 mmol) were dissolved in dichloromethane (30 mL) at 0 °C, and left to stir for 8 h. The racemic epoxide was isolated as a cream solid (0.160 g, 90%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (4:1:0.1) mixture as eluent. ν_{\max} (film)/cm⁻¹: 3057, 2903, 2223, 1610, 1577, 1491, 1242, 997. ¹H NMR (300 MHz, CDCl₃): δ_{H} 3.94 (1H, dd, *J* = 4, 1 Hz), 4.08 (1H, d, *J* = 4 Hz), 5.73

(1H, s), 6.93 (1H, d, *J* = 9 Hz), 7.28–7.39 (5H, m), 7.58 (1H, dd, *J* = 9, 2 Hz), 7.74 (1H, d, *J* = 2 Hz) (*only trans* observed). ¹³C NMR (75 MHz, CDCl₃): δ_{C} : 48.5, 58.2, 75.2, 104.7, 118.6, 118.9, 121.3, 127.0, 129.1, 129.3, 134.0, 134.8, 136.3, 156.1. HRMS *m/z*: 250.0859 [M + H]⁺; [C₁₆H₁₁NO₂ + H]⁺ requires 250.0863. HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 29.21 min (48.01%), 38.23 min (51.99%).

Using General Procedure B. Tetraphenylphosphonium monoperoxysulfate (3.61 g, 8.0 mmol) and iminium salt **3** (0.144 g, 0.2 mmol) were dissolved in chloroform (100 mL) and cooled to –30 °C. 6-Cyano-2-phenyl-chromene **15b** (0.47 g, 2.0 mmol) dissolved in chloroform (10 mL) was then added slowly over 10 min to the reaction mixture. The reaction was quenched at 37% conversion, and enantioenriched 6-cyano-2-phenyl-chromene epoxide was isolated as a cream solid (0.12 g, 24%; mp = 136–138 °C) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (4:1:0.1) mixture as eluent. [α_{D}] = +72°, (*c* 0.01 g/mL, CH₂Cl₂); HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 26.23 min (88.99%), 34.17 min (11.01%).

6-Nitro-2-isopropyl-chromene Epoxide 20a. *Using General Procedure A.* 6-Nitro-2-isopropyl-chromene **16a** (0.26 g, 1.2 mmol) and *meta*-chloroperbenzoic acid (0.2 g, 1.2 mmol) were dissolved in dichloromethane (50 mL) at 0 °C, and left to stir for 8 h. The racemic epoxide was isolated as a yellow oil (0.14 g, 50%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (5:1:0.1) mixture as eluent. ν_{\max} (film)/cm⁻¹: 2965, 2923, 1620, 1591, 1520, 1486, 1341, 1256, 1089. ¹H NMR (400 MHz, CDCl₃): δ_{H} 0.97 (6H, d, *J* = 9 Hz, *cis* or *trans*), 1.09 (6H, d, *J* = 9 Hz, *cis* or *trans*), 1.99–2.09 (1H, m, *trans*), 2.20–2.28 (1H, m, *cis*), 3.73 (1H, dd, *J* = 6, 1 Hz, *trans*), 3.85 (1H, d, *J* = 6 Hz, *cis*), 3.94 (1H, d, *J* = 6 Hz, *cis*), 3.96 (1H, d, *J* = 6 Hz, *trans*), 4.00 (1H, d, *J* = 8 Hz, *cis*), 4.47 (1H, d, *J* = 8 Hz, *trans*), 6.91 (1H, d, *J* = 12 Hz, *trans*), 6.94 (1H, d, *J* = 12 Hz, *cis*), 8.15 (2H, dd, *J* = 12, 4 Hz, C7-H, *cis* and *trans*), 8.28 (1H, d, *J* = 4 Hz, *trans*), 8.31 (1H, d, *J* = 4 Hz, *cis*) (ratio of *trans*:*cis*, 4:1). ¹³C NMR (75 MHz, CDCl₃): δ_{C} : 18.2, 18.3, 18.4, 19.1, 31.5, 31.8, 48.5, 48.7, 56.2, 56.9, 78.1, 78.8, 117.9, 118.2, 120.6, 121.0, 126.1, 126.2, 126.3, 126.7, 141.4, 159.0, 160.2, 169.5. HRMS *m/z*: 236.0915 [M + H]⁺; [C₁₂H₁₃NO₄ + H]⁺ requires 236.0918. HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 35.78 min (8.19%, *cis*), 52.39 min (9.52%, *cis*), 60.19 min (41.27%, *trans*), 65.78 min (41.02%, *trans*).

Using General Procedure B. Tetraphenylphosphonium monoperoxysulfate (1.17 g, 2.6 mmol) and iminium salt **3** (0.046 g, 0.065 mmol) were dissolved in chloroform (30 mL) and cooled to –30 °C. 6-Nitro-2-isopropyl-chromene **16a** (0.14 g, 0.65 mmol) dissolved in chloroform (3 mL) was then added slowly over 10 min to the reaction mixture. The reaction was quenched at 38% conversion, and enantioenriched 6-nitro-2-isopropyl-chromene epoxide was isolated as a yellow oil (0.035 g, 25%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (5:1:0.1) mixture as eluent. [α_{D}] = –63°, (*c* 0.004 g/mL, CH₂Cl₂). HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 35.74 min (0.73%, *cis*), 56.13 min (7.46%, *cis*), 63.05 min (11.07%, *trans*), 68.42 min (80.73%, *trans*).

6-Cyano-2-isopropyl-chromene Epoxide 20b. *Using General Procedure A.* 6-Cyano-2-isopropyl-chromene **16b** (0.29 g, 1.44 mmol) and *meta*-chloroperbenzoic acid (0.25 g, 1.44 mmol) were dissolved in dichloromethane (60 mL) at 0 °C, and left to stir for 5 h. The racemic epoxide was isolated as a colorless oil (0.17 g, 55%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (5:1:0.1) mixture as eluent. ν_{\max} (film)/cm⁻¹: 2967, 2932, 2877, 2226, 1616, 1582, 1495, 1251, 1134, 1008, 876. ¹H NMR (400 MHz, CDCl₃): δ_{H} 0.97 (6H, d, *J* = 7 Hz, *cis* or *trans*), 1.08 (6H, d, *J* = 7 Hz, *cis* or *trans*), 1.97–2.06 (1H, m, *trans*), 2.20–2.27 (1H, m, *cis*), 3.72 (1H, dd, *J* = 4, 1 Hz, *trans*), 3.83 (1H, d, *J* = 4 Hz, *cis*), 3.87 (1H, d, *J* = 4 Hz, *cis*), 3.89 (1H, d, *J* = 4 Hz, *trans*), 3.95 (1H, d, *J* = 6 Hz, *cis*), 4.42 (1H, d, *J* = 6 Hz, *trans*), 6.89 (2H, d, *J* = 9 Hz, *cis* and *trans*), 7.53 (2H, dd, *J* = 9, 2 Hz, *cis* and *trans*), 7.63 (1H, d, *J* = 2 Hz, *trans*), 7.67 (1H, d, *J* = 2 Hz, *cis*) (ratio of *trans*:*cis* 4:1). ¹³C NMR (100 MHz, CDCl₃): δ_{C} : 18.7, 19.3, 31.5, 48.6, 56.6, 77.8, 78.5, 118.5, 118.9, 134.2, 134.8. HRMS *m/z*: 216.1021 [M + H]⁺; [C₁₃H₁₃NO₂ +

H]⁺ requires 216.1022. HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 42.44 min (10.10%), 64.01 min (39.00%), 80.14 min (9.96%), 84.10 min (40.94%).

Using General Procedure B. Tetraphenylphosphonium monoperoxysulfate (27.4 g, 60.8 mmol) and iminium salt **3** (1.09 g, 1.52 mmol) were dissolved in chloroform (300 mL) and cooled to $-30\text{ }^{\circ}\text{C}$. 6-Cyano-2-isopropyl-chromene **16b** (3.0 g, 15.2 mmol) dissolved in chloroform (30 mL) was then added slowly over 10 min to the reaction mixture. The reaction was quenched at 36% conversion, and enantioenriched 6-cyano-2-isopropyl-chromene epoxide was isolated as a colorless oil (0.75 g, 23%) after purification by column chromatography using a petroleum ether/ethyl acetate/triethylamine (5:1:0.1) mixture as eluent. $[\alpha]_{\text{D}} = -52^{\circ}$, (*c* 0.01 g/mL, CH_2Cl_2). HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 43.17 min (0.12%), 71.15 min (17.11%), 81.47 min (5.04%), 89.15 min (77.73%).

Formation of Alcohol (+)-23.⁴⁵ Epoxide (+)-**19b** (1 g, 4.02 mmol) was dissolved in anhydrous methanol (50 mL) in a flame-dried round-bottom flask. The solution was then purged with nitrogen, and a catalytic amount of palladium/carbon was added to the stirring solution, followed by the addition of hydrogen gas (1 atm). The reaction was allowed to stir at room temperature, with the reaction progress monitored by thin-layer chromatography. Upon reaction completion, the reaction mixture was filtered through Celite, and remaining organic solvents were removed under reduced pressure. Alcohol **23** (1 g, 99%) was isolated as a colorless oil after column chromatography using a petroleum ether/ethyl acetate (1:1) mixture as eluent. $[\alpha]_{\text{D}} = +28.0^{\circ}$ (*c* 0.01 g/mL, CH_2Cl_2). ν_{max} (film)/ cm^{-1} : 3424, 2224, 1579, 1492, 1245. ^1H NMR (400 MHz, CDCl_3): 1.84 (1H, d, *J* = 4 Hz), 2.92 (1H, dd, *J* = 16, 9 Hz), 3.09 (1H, dd, *J* = 16, 5 Hz), 4.08–4.22 (1H, m), 4.91 (1H, d, *J* = 8 Hz), 6.99 (1H, d, *J* = 8 Hz), 7.35–7.49 (7H, m). ^{13}C NMR (100 MHz, CDCl_3): 32.2, 67.4, 82.4, 104.4, 117.6, 119.1, 121.5, 126.9, 129.0, 129.1, 132.0, 134.4, 137.1, 157.7; *m/z* found $[\text{M} + \text{Na}]^+$ 274.0842; $[\text{C}_{16}\text{H}_{13}\text{NO}_2 + \text{Na}]^+$ requires 274.0838.

Formation of (10S)-Camphorsulfonyl Ester (+)-24.⁴⁶ Alcohol **23** (1.0 g, 1 equiv, 3.98 mmol), (10S)-(+)-camphorsulfonyl chloride (996 mg, 1 equiv, 3.98 mmol) and dry toluene (50 mL) were added to a flame-dried round-bottom flask under nitrogen. To the stirring solution, triethylamine (1.1 mL, 2 equiv, 7.96 mmol) was slowly added, and left to stir for 24 h. Upon reaction completion, excess organic solvents were removed under reduced pressure. Purification by column chromatography using a petroleum ether/ethyl acetate (6:1) mixture as eluent afforded colorless crystalline **28**. Slow recrystallization from dichloromethane/hexane afforded ester **24** (6-cyano-(2R)-phenyl-(3S)-camphor(16S,19R)-sulfonyl ester chromene), as long colorless crystals (0.8 g, 43%; mp = 153–155 $^{\circ}\text{C}$). $[\alpha]_{\text{D}} = +44.0^{\circ}$ (*c* 0.02 g/mL, CH_2Cl_2). ν_{max} (film)/ cm^{-1} : 2963, 2226, 1743, 1493, 1246, 906, 726. ^1H NMR (400 MHz, CDCl_3): 0.77 (3H, s), 0.98 (3H, s), 1.35–1.41 (1H, m), 1.52–1.59 (1H, m), 1.88–2.01 (2H, m), 2.08 (1H, t, *J* = 4 Hz), 2.22–2.37 (2H, m), 2.65 (1H, d, *J* = 15 Hz), 3.11 (2H, m), 3.35 (1H, d, *J* = 15 Hz), 5.22–5.25 (1H, m), 5.45 (1H, d, *J* = 5 Hz), 7.05 (1H, d, *J* = 9 Hz), 7.33–7.38 (6H, m), 7.48 (1H, d, *J* = 9 Hz). ^{13}C NMR (100 MHz, CDCl_3): 19.6, 19.7, 24.9, 26.8, 28.9, 42.4, 42.7, 47.9, 48.3, 57.9, 75.3, 78.9, 104.7, 117.6, 118.9, 119.5, 126.0, 129.0, 129.1, 132.4, 134.2, 136.7, 157.0, 214.0; *m/z* found $[\text{M} + \text{NH}_4]^+$: 483.1945; $[\text{C}_{26}\text{H}_{27}\text{NO}_5\text{S} + \text{NH}_4]^+$ requires 483.1948.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra; chromatograms and spectra for ee determination by GC, HPLC, and NMR techniques; X-ray data and ORTEP figure for **24**, including CIF files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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