Kinetic resolution in asymmetric epoxidation using iminium salt catalysis

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Metadata Record: https://dspace.lboro.ac.uk/2134/16803

Version: Published

Publisher: American Chemical Society

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Kinetic Resolution in Asymmetric Epoxidation using Iminium Salt Catalysis

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* Supporting Information

ABSTRACT: The first reported examples of kinetic resolution in epoxidation reactions using iminium salt catalysis are described, providing up to 99% ee in the epoxidation of racemic cis-chromenes.

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 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 (TPPPP)15 as the oxidant.16 We have used the process, for example, in the syntheses of levocromakalim 4,17 (−)-lomatim 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

Figure 1. Iminium salt catalysts.
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), 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, Jacobsen, Katsuki, and Shi.

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 2H-chromenes, including inter alia: via an allene intermediate through a Claisen rearrangement, oxidation of allylphenols, iodination of allylphenols, using metal phenoxides and carbonyls, using palladium catalysis, dehydration of chromenols, using the Wittig reaction, using metathesis, and using the Petasis reaction.

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. 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 (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.

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...
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. 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, 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 catechins, in quantitative yield. Alcohol 23 was then converted to the corresponding sulfonyl ester 24 by treatment with 10S-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 Chiracel OD-H 5 μm particle size column. All HPLC samples were run using hexane–isopropanol mixtures as eluent.

**General Procedure for Acetal Formation.** 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 × 20 mL), the solution dried over magnesium sulfate, and the organic solvents were removed under

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

<table>
<thead>
<tr>
<th>starting material</th>
<th>conversion (%)</th>
<th>epoxide</th>
<th>epoxide d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>100</td>
<td>(+)-17a</td>
<td>2:1</td>
</tr>
<tr>
<td>13b</td>
<td>100</td>
<td>(+)-17b</td>
<td>1:1</td>
</tr>
<tr>
<td>14a</td>
<td>100</td>
<td>(+)-18a</td>
<td>2:1</td>
</tr>
<tr>
<td>14b</td>
<td>100</td>
<td>(+)-18b</td>
<td>3.5:1</td>
</tr>
<tr>
<td>15a</td>
<td>100</td>
<td>(+)-19a</td>
<td>trans only</td>
</tr>
<tr>
<td>15b</td>
<td>100</td>
<td>(+)-19b</td>
<td>trans only</td>
</tr>
<tr>
<td>16a</td>
<td>81</td>
<td>(+)-20a</td>
<td>4:1</td>
</tr>
<tr>
<td>16b</td>
<td>80</td>
<td>(+)-20b</td>
<td>4:1</td>
</tr>
</tbody>
</table>

**Scheme 3**

Reagents 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.
The chromene and the corresponding acetal (1 equiv) were added. The reaction mixture was heated under reflux until completion. The reaction mixture was filtered through Celite and washed with diethyl ether. Conversion was determined from the $^{1}H$ NMR spectra of the crude reaction mixture.

**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. The reaction mixture was slowly over 10 min to the reaction mixture. The reaction progress was monitored by $^{1}H$ 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.

**General Procedure for the Formation of Chiral Epoxides.** Tetraphenylphosphonium monopersulfate (4 equiv) and iminium salt (10 mol %) were dissolved in chloroform (2 mL per 0.1 g of chromene). The reaction mixture was then added slowly over 10 min to the reaction mixture. The reaction progress was monitored by $^{1}H$ 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.

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

<table>
<thead>
<tr>
<th>starting material</th>
<th>conv. (%)</th>
<th>epoxide</th>
<th>epoxide d.r. (trans:cis)</th>
<th>major epoxide</th>
<th>trans-diastereoisomer ee (%)</th>
<th>minor epoxide</th>
<th>cis-diastereoisomer ee (%)</th>
<th>recovered chromene ee (%)</th>
<th>$k_{ml}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>48</td>
<td>(−)-17a</td>
<td>2.5:1</td>
<td>87</td>
<td>97</td>
<td>26</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13b</td>
<td>52</td>
<td>(−)-17b</td>
<td>3:1</td>
<td>86</td>
<td>97</td>
<td>37</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14a</td>
<td>50</td>
<td>(−)-18a</td>
<td>4:1</td>
<td>87</td>
<td>98</td>
<td>40</td>
<td>3.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14b</td>
<td>56</td>
<td>(−)-18b</td>
<td>3.5:1</td>
<td>73</td>
<td>92</td>
<td>41</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15a</td>
<td>26</td>
<td>(+)-19a</td>
<td>trans only</td>
<td>76</td>
<td></td>
<td>17</td>
<td>3.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15b</td>
<td>37</td>
<td>(+)-19b</td>
<td>trans only</td>
<td>74</td>
<td></td>
<td>14</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16a</td>
<td>38</td>
<td>(−)-20a</td>
<td>10:1</td>
<td>76</td>
<td>82</td>
<td>42</td>
<td>8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16b</td>
<td>36</td>
<td>(−)-20b</td>
<td>16:1</td>
<td>88</td>
<td></td>
<td>50</td>
<td>27.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^{a}$All reactions were carried out with substrate (1 equiv), catalyst (10 mol %), and tetraphenylphosphonium monopersulfate (TPPS) (4 equiv) in CHCl$_3$ at −30 °C.$^{b}$Conversion was determined from the $^{1}H$ NMR spectra of the crude reaction mixture. $^{c}$Enantioselectivity was determined using chiral stationary phase HPLC with a Chiralcel OD-H column. $^{d}$Diastereoisomeric ratios were determined from the $^{1}H$ NMR spectra of the reaction mixture after workup. $^{e}$Enantiomeric excess was calculated by ($1-C$)/(1 + ee) and C is the fraction of 13, 14, 15, or 16 consumed and ee is the percentage enantiomeric excess/100.$^{21,22,36}$

**Scheme 4**

**The Journal of Organic Chemistry**

![Article](dx.doi.org/10.1021/jo401345m) J. Org. Chem. 2013, 78, 8074–8082

![Image](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAEAAAABcCAIAAADQc+1AAAAA3NCSVQICAItCPk绿水 systemic risk for a system exhibit...@)
purification by vacuum distillation (2 mbar, 42–45 °C). 1H NMR (300 MHz, CDCl3): δH 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). 13C NMR (75 MHz, CDCl3): δC 14.5, 21.4, 30.0, 60.0, 101.3, 121.4, 156.8. 6-Nitro-2-methyl-chromene 13a. Compound (13a) was prepared using the general procedure for chromene formation from 4-nitrophenol (3.19 g, 23.0 mmol) and 1,1-diethoxy-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). After purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. δνmax (film)/cm⁻¹: 1575, 1506, 1480, 1373, 911. 1H NMR (300 MHz, CDCl3): δH 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 = 9, 3 Hz). 13C NMR (75 MHz, CDCl3): δC 22.0, 73.2, 116.4, 121.4, 122.3, 125.5, 128.7, 159.2. HRMS m/z: 191.0577 [M⁺]; C₉H₁₀NO₂ requires 191.0576. HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 5.7 min (48.76%), 5.97 min (51.24%).

Cyano-2-methyl-chromene 13b. Compound (13b) was prepared using the general procedure for chromene formation from 4-cyanophenol (1.65 g, 13.99 mmol) and 1,1-diethoxy-2-ene 9 (1.0 g, 6.93 mmol), yielding compound (13b) as a cream solid (0.90 g, 76%; mp = 53–55 °C). After purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. δνmax (film)/cm⁻¹: 3063, 3034, 1647, 1612, 1576, 1480, 1343, 1261, 913. 1H NMR (300 MHz, CDCl3): δH 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). 13C NMR (75 MHz, CDCl3): δC 87.5, 116.3, 120.9, 122.3, 124.7, 125.1, 127.2, 129.0, 129.1, 133.5, 141.8, 158.6. m/z: 254.0799 [M + H⁺]; C₁₀H₅NO⁺ requires 254.0812. HPLC trace (95:5 hexane/isopropanol, 0.5 mL/min); 23.55 min (49.20%), 24.66 min (50.80%).

6-Chloro-2-methyl-chromene 13c. Compound (13c) was prepared using the general procedure for chromene formation from 6-chlorophenol (2.95 g, 23.04 mmol) and 1,1-diethoxy-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. δνmax (film)/cm⁻¹: 3050, 2977, 2932, 1767, 1645, 1481, 1368, 1208. 1H NMR (300 MHz, CDCl3): δH 4.44 (1H, d, J = 7 Hz), 4.95–5.03 (1H, m), 5.70 (1H, dd, J = 10, 3 Hz), 6.51 (1H, dd, J = 10, 2 Hz), 6.71 (1H, d, J = 9, 3 Hz), 6.94 (1H, dd, J = 3, 2 Hz), 7.05 (1H, dd, J = 9, 3 Hz). 13C NMR (75 MHz, CDCl3): δC 21.4, 71.8, 117.5, 123.0, 123.3, 125.8, 128.6, 128.4, 158.2, 152.2. HRMS m/z: 180.0338 [M⁺]; C₁₀H₈ClO 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-diethoxy-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. δνmax (film)/cm⁻¹: 2961, 1614, 1580, 1515, 1483, 1342, 1242, 1091, 1002, 747. 1H NMR (400 MHz, CDCl3): δH 0.96 (6H, t, J = 7 Hz, 1.40–1.45 (8H, 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). 13C NMR (100 MHz, CDCl3): 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 [M + H⁺]; C₁₀H₈NO⁺ requires 220.0968. HPLC trace (90:10 hexane/isopropanol, 1 mL/min); 4.89 min (49.49%), 5.18 min (50.51%).

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-diethoxy-2-ene 9 (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. δνmax (film)/cm⁻¹: 3032, 1639, 1477, 1424, 1368, 1261, 1231, 1200, 1121, 1034, 814, 755, 697. 1H NMR (300 MHz, CDCl3): δH 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, dd, J = 3, 2 Hz), 7.08 (1H, dd, J = 9, 3 Hz), 7.37–7.49 (5H, m). 13C NMR (75 MHz, CDCl3): δC 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 [M + H⁺]; C₁₂H₁₀ClO⁺ requires 243.0571. HPLC trace (99:1 hexane/isopropanol, 0.25 mL/min); inseparable: 104.77 min (100%).

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. \( \nu_{\text{KBr}} \) (film)/cm\(^{-1} \): 3073, 2965, 2874, 1613, 1579, 1325, 1241, 1089. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.03 (1H, dd, \( J = 7, 3 \) Hz), 6.95–2.03 (1H, m), 5.77 (1H, dd, \( J = 10, 3 \) Hz), 4.63 (1H, dd, \( J = 10, 2 \) Hz), 6.77 (1H, dd, \( J = 9 \) Hz), 7.81 (1H, dd, \( J = 3 \) Hz), 7.97 (1H, dd, \( J = 9, 3 \) Hz). \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): \( \delta \) 171.1, 176.4, 82.4, 81.6, 115.9, 121.5, 122.2, 123.1, 125.5, 126.1, 141.5, 160.0. m/z: 237.1229 [M + NH\(_4\)]\(^+\); [C\(_{12}\)H\(_{13}\)NO\(_3\) + NH\(_4\)]\(^+\) requires 237.1234. HPLC trace (90:10 hexane/isopropanol, 1 ml/min); 4.84 min (49.81%), 5.12 min (51.09%).

6-Cyano-2-isopropyl-chromene 16b. Compound (16b) was prepared using the general procedure for chromene formation from 4-cyanochromen-9(1H) (8.9 g, 91 mmol) and 1,4-diethoxy-4-methylpent-2-en-12 (6.7 g, 45 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. \( \nu_{\text{KBr}} \) (film)/cm\(^{-1} \): 3053, 2965, 2931, 2874, 2225, 1603, 1489, 1379, 1252, 1130. \(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 0.97 (6H, d, \( J = 7, 5 \) 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). \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): \( \delta \) 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 [M + H]+; [C\(_{13}\)H\(_{13}\)NO\(_3\) + H]+ requires 200.1070. HPLC trace (90:10 hexane/isopropanol, 1 ml/min); 5.02 min (49.9%), 5.42 min (50.1%).

6-Chloro-2-isopropyl-chromene 16c. Compound (16c) was prepared using the general procedure for chromene formation from 4-chlorochromen-9(1H) (1.5 g, 12.4 mmol) and 1,4-diethoxy-4-methylpent-2-en-12 (1.06 g, 6.2 mmol), yielding compound (16c) as a colorless oil (0.21 g, 45%) after purification by column chromatography using a petroleum ether/toluene (3:2) mixture as eluent. \( \nu_{\text{KBr}} \) (film)/cm\(^{-1} \): 3050, 2963, 2931, 2873, 1637, 1481, 1234, 1203, 1123, 1019, 977, 878, 814, 698. \(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 1.10 (6H, d, \( J = 7, 1 \) 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, \( J = 9 \) Hz), 6.92 (1H, d, \( J = 3 \) Hz), 7.03 (1H, dd, \( J = 9, 3 \) Hz). \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): \( \delta \) 17.5, 17.6, 33.4, 80.2, 116.2, 123.3, 123.6, 125.3, 125.6, 126.0, 128.7. 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 17a (0.20 g, 90%; mp = 86 °C). The racemic epoxide was isolated as a cream solid (0.20 g, 90%; mp = 86 °C). The racemic epoxide was isolated as a cream solid (0.20 g, 90%; mp = 86 °C). The racemic epoxide was isolated as a cream solid (0.20 g, 90%; mp = 86 °C). The racemic epoxide was isolated as a cream solid (0.20 g, 90%; mp = 86 °C).
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/dichloromethane/triethylamine (5:1:0.1) mixture as eluent. \( \nu_{\text{max}} \) (film/cm\(^{-1} \)) 2963, 2925, 2224, 1745, 1610, 1579, 1494, 1247, 1170. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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), 7.25–7.23 (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). \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): \( \delta \) 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, 143.6, 156.0. HRMS m/z: 238.0840 \([M + Na]^+\); \([C_7H_7NO_3 + Na]^+\) 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. Tetrabutylphosphonium monoper-
osulfate (3.36 g, 7.44 mmol) and iminium salt (0.13 g, 0.182 mL) were added to the reaction mixture. The reaction was quenched at 35% conversion, and enantioenriched 6-cyano-2-propyl-chromene epoxide was isolated as a colorless oil (0.13 g, 91%) after purification by column chromatography using a petroleum ether/dichloromethane/triethylamine (5:1:0.1) mixture as eluent. \( \epsilon_{[\%]} = 19\), \( c = 0.004 \text{g/mL}, \text{CHCl}_3\); HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min), 32.44 min (10.93%), 36.17 min (10.56%), 36.73 min (21.42%), 39.38 min (67.09%).

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 (0.19 g, 50%) after purification by column chromatography using a petroleum ether/dichloromethane/triethylamine (5:1:0.1) mixture as eluent.

1. C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 12.8, 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 \([M + H]^+\); \([C_7H_7NO_3 + H]^+\) 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. Tetrabutylphosphonium monoper-
osulfate (3.17 g, 6.2 mmol) and iminium salt (0.19 g, 0.69 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 (0.19 g, 50%) after purification by column chromatography using a petroleum ether/dichloromethane/triethylamine (5:1:0.1) mixture as eluent. \( \epsilon_{[\%]} = -53\), \( c = 0.004 \text{g/mL}, \text{CHCl}_3\); 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).
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 monoper-oxysulfate (27.4 g, 60.8 mmol) and iminum salt 3 (1.09 g, 1.52 mmol) were dissolved in chloroform (300 mL) and cooled to −30 °C. 6-Cyano-2-isopropyl-chromene 16b (3.0 g, 1.52 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. [α]D = −52° (c 0.01 g/mL, CH2Cl2).

HPLC trace (99.5:0.5 hexane/isopropanol, 0.5 mL/min); 43.17 min (0.12%), 71.15 min (17.11%), 84.57 min (5.04%), 89.15 min (77.73%).

Formation of Alcohol (+)-23.45 Epoxide (+)-19b (1 g, 4.02 mmol) was dissolved in chloroform (300 mL) and cooled to −30 °C. 

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REFERENCES


