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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 ozone.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 levcromakalim 4,17 (−)-lomatrin 5 and (+)-trans-khellactone 6,18 and scutellorin,19 utilizing iminium salt catalysts 1 and 3 (Figure 2). Kinetic resolution in these iminium salt-catalyzed epoxidation processes has not...
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 $13−16$ (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 $^1$H NMR spectroscopy carried out on the inseparable mixture of diastereoisomers, and ranged from 1:1 to exclusively $trans$ with increasing bulk of the $R^1$ substituent at C2. Decomposition was observed when chromenes containing a chloro $R^2$ 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 $(\pm)$-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 $^1$H NMR spectroscopic data of the mixture of inseparable

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

Table 1. Synthesis of Racemic C6-Substituted Chromenes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$13a$</td>
<td>$NO_2$</td>
</tr>
<tr>
<td>$13b$</td>
<td>$R=CN$</td>
</tr>
<tr>
<td>$13c$</td>
<td>$R=Cl$</td>
</tr>
<tr>
<td>$14a$</td>
<td>$NO_2$</td>
</tr>
<tr>
<td>$14b$</td>
<td>$CN$</td>
</tr>
<tr>
<td>$14c$</td>
<td>$Cl$</td>
</tr>
<tr>
<td>$15a$</td>
<td>$NO_2$</td>
</tr>
<tr>
<td>$15b$</td>
<td>$CN$</td>
</tr>
<tr>
<td>$15c$</td>
<td>$Cl$</td>
</tr>
<tr>
<td>$16a$</td>
<td>$NO_2$</td>
</tr>
<tr>
<td>$16b$</td>
<td>$CN$</td>
</tr>
<tr>
<td>$16c$</td>
<td>$Cl$</td>
</tr>
</tbody>
</table>
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 material, 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
The chromene and eluent, yielding the chromene as a pure crystalline or oily product. Column chromatography using a petroleum ether/toluene mixture as 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 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 further 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 monoperoxysulfate (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 olefin (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.

Reagents and conditions: (i) Pd/C, H2 (1 atm), MeOH, r.t., 20 min, quantitative yield; (ii) (10 mol %), PhMe, r.t., 24 h, 43%.

Diastereoisomeric ratios were determined from the 1H NMR spectra of the reaction mixture after workup. krel = 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.

### Table 3. Kinetic Resolution of Olefins Using Asymmetric Epoxidation Mediated Using Catalyst 3\(^a\)

<table>
<thead>
<tr>
<th>starting material</th>
<th>conv. (%)(^b)</th>
<th>epoxide</th>
<th>epoxide d.r. (trans/cis)(^c)</th>
<th>major epoxide</th>
<th>minor epoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>trans-diastereoisomer ee (%)(^d)</td>
<td>cis-diastereoisomer ee (%)(^d)</td>
</tr>
<tr>
<td>13a</td>
<td>48</td>
<td>(−)-17a</td>
<td>2.5:1</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td>13b</td>
<td>52</td>
<td>(−)-17b</td>
<td>3:1</td>
<td>86</td>
<td>97</td>
</tr>
<tr>
<td>14a</td>
<td>50</td>
<td>(−)-18a</td>
<td>4:1</td>
<td>87</td>
<td>98</td>
</tr>
<tr>
<td>14b</td>
<td>56</td>
<td>(−)-18b</td>
<td>3.5:1</td>
<td>73</td>
<td>92</td>
</tr>
<tr>
<td>15a</td>
<td>26</td>
<td>(+)-19a</td>
<td>trans only</td>
<td>76</td>
<td>17</td>
</tr>
<tr>
<td>15b</td>
<td>37</td>
<td>(+)-19b</td>
<td>trans only</td>
<td>74</td>
<td>14</td>
</tr>
<tr>
<td>16a</td>
<td>38</td>
<td>(−)-20a</td>
<td>10:1</td>
<td>82</td>
<td>42</td>
</tr>
<tr>
<td>16b</td>
<td>36</td>
<td>(−)-20b</td>
<td>16:1</td>
<td>99</td>
<td>50</td>
</tr>
</tbody>
</table>

\(^a\)All reactions were carried out with substrate (1 equiv), catalyst (10 mol%), and tetraphenylphosphonium monoperoxysulfate (TPPP) (4 equiv) in CHCl\(_3\) at −30 °C. \(^b\)Conversion was determined from the 1H NMR spectra of the crude reaction mixture. \(^c\)Enantioselectivity was determined using chiral stationary phase HPLC with a Chiracel OD-H column. \(^d\)Diastereoisometric ratios were determined from the 1H NMR spectra of the reaction mixture after workup. krel = 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.

### Scheme 4\(^a\)

\(^a\)Reagents and conditions: (i) Pd/C, H\(_2\) (1 atm), MeOH, r.t., 20 min, quantitative yield; (ii) (10 mol %), PhMe, r.t., 24 h, 43%.

...continued from previous page...

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 monoperoxysulfate (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 olefin (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 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, CDCl\(_3\)): δ\(_H\) 1.17 (6H, t, J = 7 Hz), 1.65 (3H, dd, J = 7, 2 Hz), 3.38−3.45 (2H, m), 3.30−3.61 (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, CDCl\(_3\)): δ\(_C\) 14.9, 17.2, 60.7, 101.7, 128.9, 129.5.

1,1-Diethoxyhex-2-ene was prepared using the general procedure for acetal formation from cis-2-pentenal (2.0 g, 20.4 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, CDCl\(_3\)): 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, CDCl\(_3\)): 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 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, CDCl\(_3\)): 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, CDCl\(_3\)): 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 was prepared using the general procedure for acetal formation 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, 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, 123.8. 14.0, 10.8.

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-diethoxybut-2-ene 9 (1.65 g, 11.49 mmol), yielding compound (13a) as a yellow crystalline solid (1.01 g, 46%; mp = 63–64 °C).

13C NMR (75 MHz, CDCl3): δC 12.0, 25.8, 61.5, 117.1, 123.8, 128.6, 130.4, 133.4, 157.3. HRMS m/z: 202.0655 [M + H]+; [C11H10NO + H]+ requires 202.0657.

6-Chloro-2-methyl-chromene 13c. Compound (13c) as a cream solid (0.73 g, 3.56 mmol), yielding compound (13c) as a yellow liquid (0.89 g, 43%) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. νmax (film)/cm−1: 3050, 2977, 2932, 1767, 1645, 1481, 1368, 1208. 1H NMR (300 MHz, CDCl3): δH 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, dd, J = 9, 3 Hz), 6.94 (1H, d, J = 3 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, 152.8. HRMS m/z: 180.0338 [M]+; C6H5ClO requires 180.0342. HPLC trace (98:2 hexane/isopropanol, 0.5 mL/min); inseparable: 10.20 min (100%).

6-Chloro-2-phenyl-chromene 13c. Compound (13c) as a white solid (0.86 g, 3.56 mmol), yielding compound (13c) as a white solid (0.90 g, 66%) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. νmax (film)/cm−1: 3063, 3034, 1647, 1612, 1576, 1480, 1343, 1261, 913. 1H NMR (300 MHz, CDCl3): δH 5.47 (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 78.5, 116.3, 120.9, 122.3, 124.2, 125.6, 127.2, 127.9, 128.9, 129.0, 139.5, 141.8, 158.6. m/z: 254.0799 [M + H]+; [C12H13ClO + H]+ requires 254.0812. HPLC trace (95:5 hexane/isopropanol, 0.5 mL/min); 25.55 min (49.20%), 24.66 min (50.80%).

6-Chloro-2-phenyl-chromene 15b. Compound (15b) as a white solid (0.73 g, 3.56 mmol), yielding compound (15b) as a white solid (0.86 g, 46%) after purification by column chromatography using a petroleum ether/toluene (1:1) mixture as eluent. νmax (film)/cm−1: 3033, 2222, 1677, 1602, 1570, 1489, 1374, 1251, 1229, 1126, 893, 825. 1H NMR (300 MHz, CDCl3): δH 5.47 (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 78.0, 116.3, 120.9, 122.3, 124.2, 125.6, 127.2, 127.9, 128.9, 129.0, 139.5, 141.8, 158.6. m/z: 254.0799 [M + H]+; [C12H13ClO + H]+ requires 254.0812. HPLC trace (95:5 hexane/isopropanol, 0.5 mL/min); 25.55 min (49.20%), 24.66 min (50.80%).
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. $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3073, 2965, 2874, 1613, 1579, 1353, 1214, 1089. 7 H NMR (400 MHz, CDCl$_3$): $\delta_1$ 1.00 (6H, dd, $J = 8, 7$ Hz), 1.95–2.03 (1H, m), 4.62–4.64 (1H, m), 5.77 (1H, dd, $J = 10, 3$ Hz), 6.43 (1H, dd, $J = 10, 2$ Hz), 6.77 (1H, dd, $J = 9$ Hz), 7.81 (1H, d, $J = 3$ Hz), 7.97 (1H, dd, $J = 9, 3$ Hz). 4.5°C NMR (75 MHz, CDCl$_3$): $\delta_2$ 17.1, 17.6, 34.2, 81.6, 115.9, 121.5, 122.2, 123.1, 125.5, 126.1, 140.5, 160.0. m/z: 2371229 [M + NH$_4$]+; [C$_{13}$H$_{13}$NO + NH$_4$]+ requires 200.1070. HPLC trace (90:10 hexane/isopropanol, 1 mL/min): 4.84 min (94.81%), 5.12 min (51.09%).

6-Cyano-2-isopropyl-chromene 16b. Compound (16b) was prepared using the general procedure for chromene formation from 4-cyanochromene (0.97 g, 8.11 mmol) and 1,1-dioxy-4-methylpent-2-en-1-ol (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. $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3053, 2965, 2931, 2874, 2225, 1603, 1489, 1379, 1252, 1130. 7 H NMR (300 MHz, CDCl$_3$): $\delta_1$ 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, dd, $J = 2, 7$ Hz), 7.32 (1H, dd, $J = 8, 2$ Hz). 4°C NMR (75 MHz, CDCl$_3$): $\delta_2$ 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: 20011062 [M + H]+; [C$_{13}$H$_{13}$NO + 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-chlorochromene (1.59 g, 12.4 mmol) and 1,1-dioxy-4-methylpent-2-en-1-ol (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. $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3050, 2963, 2931, 2873, 1637, 1481, 1234, 1203, 1123, 1019, 977, 878, 814, 698. 7 H NMR (300 MHz, CDCl$_3$): $\delta_1$ 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, dd, $J = 9, 6$ Hz), 6.92 (1H, d, $J = 3$ Hz), 7.03 (1H, dd, $J = 9, 3$ Hz). 4°C NMR (75 MHz, CDCl$_3$): $\delta_2$ 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 (99:0.1 hexane/isopropanol, 0.25 mL/min): 14.80 min (94.75%), 15.87 min (50.26%).

6-Nitro-2-methyl-cromene Oxide 17a. Using General Procedure A. 6-Nitro-2-methyl-cromene 17a (0.205 g, 1.07 mmol) and 3-chloroperbenzoic acid (1.10 g, 6.42 mmol) were dissolved in dichloromethane (40 mL) at 0°C, and left to stir for 6 h. The mixture was stirred slowly over 10 min to the reaction mixture. The reaction was quenched at 52% conversion, and enantiomeric 6-cyano-2-methylchromene epoxide was isolated as a yellow oil (0.031 g, 33%; bp = 77–79°C) after purification by column chromatography using a petroleum ether/ethy acetate/triethlyamine (3:1:0.1) mixture as eluent. $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2917, 2849, 2227, 1615, 1581, 1495, 1253, 1229, 1159, 873. 7 H NMR (300 MHz, CDCl$_3$): $\delta_1$ 1.33 (3H, d, $J = 7, 2$ Hz), 1.58 (3H, d, $J = 7$ Hz), 3.63 (1H, dd, $J = 4, 1$ Hz, trans), 3.69 (1H, dd, $J = 1, 4$ 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), 4.82 (1H, q, $J = 6$ Hz, trans), 6.88 (2H, d, $J = 9$ Hz, cis and trans), 7.52 (2H, dd, $J = 2, 7$ Hz, cis and trans), 7.64 (1H, d, $J = 2$ Hz, cis), 7.66 (1H, d, $J = 2$ Hz, cis). 4°C NMR (75 MHz, CDCl$_3$): $\delta_2$ 16.5, 18.4, 40.8, 49.4, 58.4, 59.1, 69.3, 69.5, 104.4, 110.4, 118.4, 118.7, 119.2, 121.1, 121.4, 133.9, 134.1, 134.3, 134.5, 155.7. HMRs m/z: 1870628 [M + H]+; C$_7$H$_7$NO$_2$ requires 187.0633. HPLC trace (99:0.5 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 18b (0.085 g, 0.5 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 enantiomeric 6-nitro-2-methyl-chromene epoxide was isolated as a yellow oil (0.031 g, 33%; bp = 77–79°C) after purification by column chromatography using a petroleum ether/ethy acetate/triethlyamine (3:1:0.1) mixture as eluent. $\alpha_e$ = −35°, (c 0.01 g/mL CHCl$_3$). HPLC trace (99:0.5 hexane/isopropanol, 0.5 mL/min): 40.45 min (0.57%), 49.52 min (17.40%), 57.23 min (72.28%), 61.39 min (9.96%).

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Article

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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/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), 7.52–7.55 (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, 3:1). \(^1^\)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, 134.6, 156.0. HRMS m/z: 238.0840 [M + Na]+; \([ \text{C}_{16}\text{H}_{12}\text{NO}_2 + \text{Na}^+ \] requires 238.0838. HPLC trace (99.50% 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 monoper-
osulfate (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 (0.36 g, 39%) after purification by column chromatography using a petroleum ether/triethylamine (5:1:0.1) mixture as eluent. \([\alpha]_{D} = -22^\circ\) (c 0.004 g/mL, CH\(_2\)Cl\(_2\)). HPLC trace (99.50% hexane/isopropanol, 0.5 mL/min); 27.10 min (0.93%), 36.17 min (10.56%), 36.73 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 °C) after purification by column chromatography using a petroleum ether/triethylamine (4:1:0.1) mixture as eluent. \([\alpha]_{D} = -22^\circ\) (c 0.004 g/mL, CH\(_2\)Cl\(_2\)). HPLC trace (99.50% hexane/isopropanol, 0.5 mL/min); 27.10 min (0.93%), 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 (0.14 g, 50%) after purification by column chromatography using a petroleum ether/triethylamine (4:1:0.1) mixture as eluent. \([\alpha]_{D} = -22^\circ\) (c 0.004 g/mL, CH\(_2\)Cl\(_2\)). HPLC trace (99.50% 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 monoper-
osulfate (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 (0.05 g) isolated as a yellow oil (0.035 g, 25%) after purification by column chromatography using a petroleum ether/triethylamine (5:1:0.1) mixture as eluent. \([\alpha]_{D} = -63^\circ\) (c 0.004 g/mL, CH\(_2\)Cl\(_2\)). HPLC trace (99.50% 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-oxidysulfate (27.4 g, 60.8 mmol) and iminium salt 3 (1.09 g, 1.52 mmol) were dissolved in chloroform (30 mL) and cooled to -30 °C for 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-chromone 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%), 84.51 min (5.09%), 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. [α]D = +28.0° (c 0.01 g/mL, CH2Cl2).

Notes

The authors declare no competing financial interest.

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REFERENCES


