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Enantioselective synthesis of chromenes

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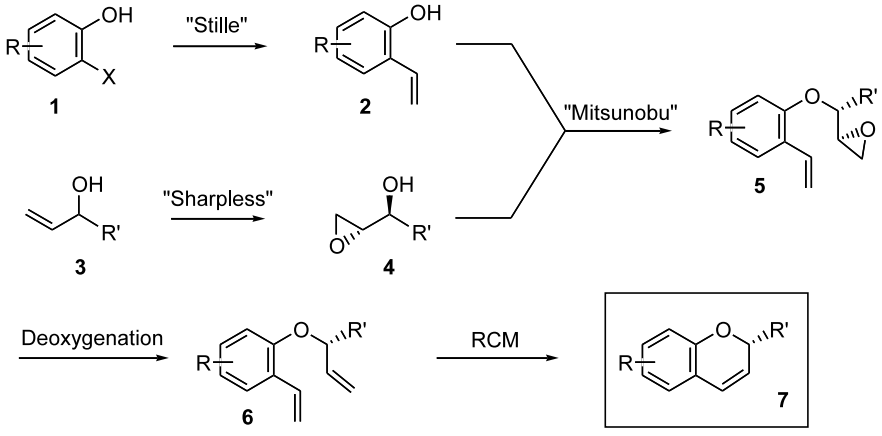
Abstract—A concise approach for the synthesis of optically active chromenes is reported. The process described herein involves, as the key steps, a Sharpless-epoxidation, a selective deoxygenation, and a ring-closing metathesis.

The chromene ring system has a central position in various classes of naturally occurring products.[1] Furthermore, many bio-active compounds (e.g. antioxidants,[2] enzyme inhibitors[3]) incorporate this key heterocycle. However, whilst the synthesis of racemic chromenes is well documented,[4] the methods available for the preparation of optically active species remain limited.[5,13] We describe in this paper our approach for the enantioselective synthesis of chromenes. Our general strategy is depicted in Scheme 1 and involved the synthesis, as starting material, of some chiral epoxyalcohols **4** and *o*-vinyl phenols **2**.

The latter compounds were prepared by Stille-olefination of the corresponding α-halogeno-phenol **1** using tributylvinyltin and $Pd_2(dba)_3{\cdot}CHCl_3$ as catalyst.[6] On the other hand, the starting epoxyalcohols **4** were synthesised by (+)-diisopropyltartrate/$Ti(OiPr)_4$/*t*-BuOOH-mediated Sharpless-kinetic resolution of variously substituted allylic alcohols **3**.[7] This afforded optically active alcohols **4** in good yield and with ee values ranging from 74 to 96% (see Table 1). Subsequent Mitsunobu reaction[8] with *o*-vinyl phenols **2** provided epoxy-ethers **5**. During this process, the epoxide served also as protecting group of the double bond, thus avoiding the well established S_N2' side reaction.[9] The epoxy-ethers **5** were then smoothly deoxygenated by Cp_2TiCl[10] to regenerate the olefinic system of **6**. The low-valent titanium^{III} complex was readily prepared by in situ reduction of Cp_2TiCl_2 by activated zinc.[11] Finally, the ring closure step was cleanly performed in nearly quantitative yield by metathesis (RCM)[12] using



Scheme 1.

Keywords: chromene; metathesis; Sharpless-epoxidation; titanium.

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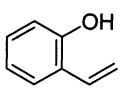
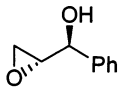
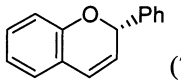
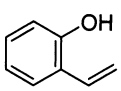
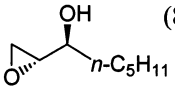
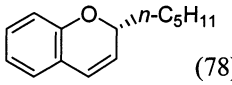
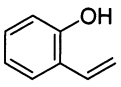
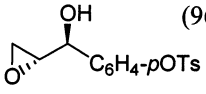
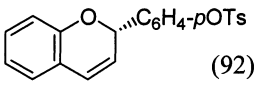
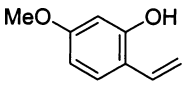
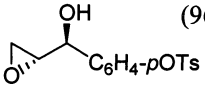
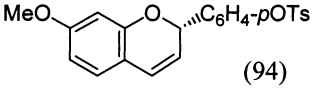
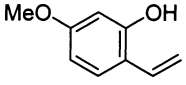
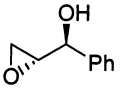
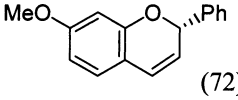
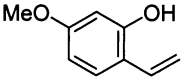
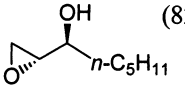
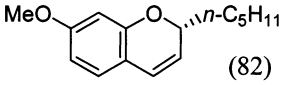
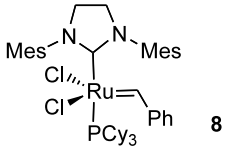
Table 1. Examples of chromene synthesis

entry	vinyl-phenol **2**	epoxy-alcohol **4** (e.e.%)[a]	yield of **5**[b] (%)	yield of **6**[b] (%)	chromene **7** (e.e.%)[a]	yield of **7**[b] (%)
a		 (74)	68	59	 (70)	94
b		 (82)	63	44	 (78)	88
c		 (96)	70	62	 (92)	92
d		 (96)	66	51	 (94)	97
e		 (74)	72	48	 (72)	89
f		 (82)	66	51	 (82)	92

[a] Enantiomeric excesses were determined by HPLC. [b] Isolated yields.



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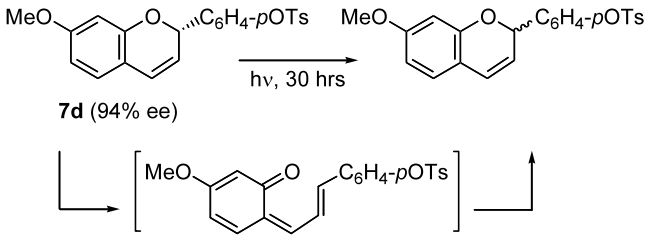
Scheme 2.



Scheme 3.

the ruthenium-based catalyst **8** (Scheme 2). Table 1 summarises the results obtained during these transformations.

It is to be noted that the overall process permits the synthesis of chiral chromenes with, in few cases, little loss of optical purity (based on the ee value of the starting alcohols **4**). However, upon irradiation with a desk light (200 W), chromene **7d** fully photoracemised in hexane within 30 h. This light-induced racemisation has already been observed by others[13] and could be attributed to a retro-Claisen rearrangement (Scheme 3).

In conclusion, we demonstrated that chromenes are readily accessible in their optically active form starting from the corresponding *o*-vinyl-phenol and Sharpless-derived α-hydroxy-epoxide. Coupling, deoxygenation and RCM furnishes chiral chromenes in overall satisfactory yield and good enantiomeric purity.[14]

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14. **A typical experimental procedure is given for the synthesis of chromene 7d**: *Synthesis of epoxy-ether **5d***: To a solution of epoxy-alcohol **4d** (96% ee, 0.069 g, 0.21 mmol, 1 equiv.) in 2 mL of THF was added, at 0°C, vinyl-phenol **2d** (0.035 g, 1.1 equiv.), PPh_3 (0.060 g, 1.1 equiv.) and DEAD (35 μL, 1.1 equiv.). The reaction was stirred at rt for 16 h and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography over silica (hexane/EtOAc: 4/1) to give epoxy-ether **5d** (oil, 0.06 g, 66% yield). ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.69 (dd, $J=2.6$ and 4.5 Hz, 1H), 2.83 (t, $J=4.5$ Hz, 1H), 3.36 (m, 1H), 3.67 (s, 3H), 4.89 (d, $J=5.8$ Hz, 1H), 5.17 (dd, $J=1.3$ and 11.2 Hz, 1H), 5.64 (dd, $J=1.3$ and 17.7 Hz, 1H), 6.21 (d, $J=2.4$ Hz, 1H), 6.46 (dd, $J=2.4$ and 8.5 Hz, 1H), 6.98 (d, $J=9.1$ Hz, 2H), 7.04 (dd, $J=11.2$ and 17.7 Hz, 1H), 7.27 (d, $J=8.6$ Hz, 2H), 7.31 (d, $J=9.1$ Hz, 2H), 7.39 (d, $J=8.5$ Hz, 1H), 7.66 (d, $J=8.6$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.6, 44.6, 54.6, 55.1, 80.8, 101.4, 106.1, 112.4, 120.5, 122.7, 127.2, 127.8, 128.3, 129.7, 131.0, 132.1, 136.1, 145.4, 149.4, 155.3, 160.0. MS (CI/NH_3), 470 (M+18, 100). *Synthesis of allylic-ether **6d***: To a mixture of Cp_2TiCl_2 (0.065 g, 2.2 equiv.) and powdered Zn (0.040 g, 5.1 equiv.) in a flame-dried flask was added 1 mL of THF. The solution was degassed under vacuum and purged with nitrogen (this operation was repeated three times). The heterogeneous solution was stirred vigorously for 45 min at rt. To the green slurry of Cp_2TiCl was added dropwise, epoxy-ether **5d** (0.055 g, 0.12 mmol, 1 equiv.) in 1 mL of THF. The solution was degassed under vacuum and purged with nitrogen (this operation was repeated three times). After 30 min, the mixture was filtered over paper and quenched with H_2O. The aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography over silica (hexane/EtOAc: 85/15) to give allylic-ether **6d** (96% ee, oil, 0.027 g, 51% yield). ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.71 (s, 3H), 5.14 (dd, $J=1.3$ and 11.2 Hz, 1H), 5.23–5.35 (m, 2H), 5.56–5.65 (m, 2H), 5.96 (m, 1H), 6.32 (d, $J=2.4$ Hz, 1H), 6.47 (dd, $J=2.4$ and 8.5 Hz, 1H), 6.96 (d, $J=8.6$ Hz, 2H), 7.01 (dd, $J=11.2$ and 17.7 Hz, 1H), 7.28 (d, $J=8.4$ Hz, 2H), 7.32 (d, $J=8.6$ Hz, 2H), 7.40 (d, $J=8.5$ Hz, 1H), 7.67 (d, $J=8.4$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.7, 55.3, 80.7, 101.8, 105.9, 112.3, 117.0, 120.8, 122, 6, 127.1, 127.8, 128.5, 129.7, 131.2, 132.4, 137.3, 139.0, 145.3, 149.1, 155.6, 160.2. MS (CI/NH_3), 454 (M+18, 100). $[\alpha]_D^{25}$ +12 (*c* 0.16, CH_2Cl_2). *Synthesis of chromene **7d***: To a solution of diene **6d** (0.013 g, 0.03 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) was added **8** (0.001 g, 0.04 equiv.). The reaction mixture was stirred at rt overnight in the dark and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography over silica (hexane/EtOAc: 4/1) to give the chromene **7d** (94% ee, oil, 0.012 g, 97% yield). ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.72 (s, 3H), 5.58 (dd, $J=3.3$ and 10.0 Hz, 1H), 5.81 (m, 1H), 6.34 (d, $J=2.4$ Hz, 1H), 6.41 (dd, $J=2.4$ and 8.3 Hz, 1H), 6.46 (dd, $J=1.8$ and 9.9 Hz, 1H), 6.89 (d, $J=7.9$ Hz, 1H), 6.95 (d, $J=8.5$ Hz, 2H), 7.28 (d, $J=8.0$ Hz, 2H), 7.34 (d, $J=8.5$ Hz, 2H), 7.68 (d, $J=8.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.6, 55.2, 76.2, 101.8, 107.0, 114.4, 121.2, 122.4, 123.9, 127.3, 128.2, 128.4, 129.7, 132.3, 139.8, 145.4, 149.3, 154.0, 160.9. MS (CI/NH_3), 409 (M+1, 100). HRMS calcd for $C_{23}H_{20}O_5S$ $(M)^+$ 408.1031, found 408.1066. IR (neat): 866, 1153, 1177, 1198, 1373, 1503, 1598, 1615, 1738, 2937.