Enantioselective Synthesis of Chromanes by Iridium-Catalyzed Asymmetric Hydrogenation of 4*H*-Chromenes

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Abstract: Iridium complexes of chiral oxazoline-based P,N-ligands proved to be efficient catalysts for the enantioselective hydrogenation of 2-aryl- and 2-alkyl-4*H*-chromenes. The best results were obtained with a ligand derived from threonine (ThrePHOX), which induced ee values of 95% to >99% in the hydrogenation of 2-methyl-, 2-cyclohexyl- and various 2-aryl-substituted chromenes.

Key words: asymmetric hydrogenation, iridium, P,N-ligands, flavanes, chromanes

Chiral chromanes, especially the 2-aryl-substituted derivatives known as flavanes, occur in many plants and exhibit a wide spectrum of biological activities. Because of their pharmacological properties, numerous synthetic derivatives have been prepared and studied as drug candidates. Representative examples are tupichinol C, used in Chinese folk medicine;[1] tephrowatsin E, isolated from the aerial parts of tephrosia watsoniana;[2] and BW683C, a potent inhibitor of rhinovirus replication in vitro[3] (see Figure 1).

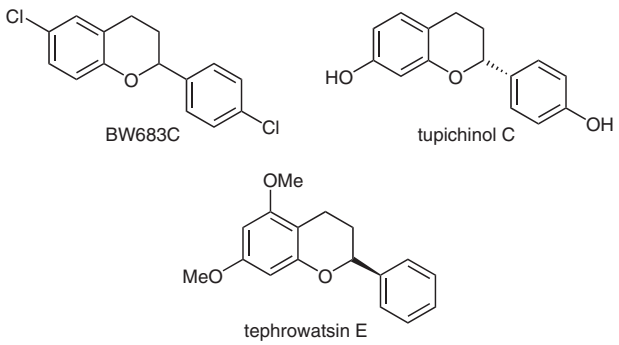
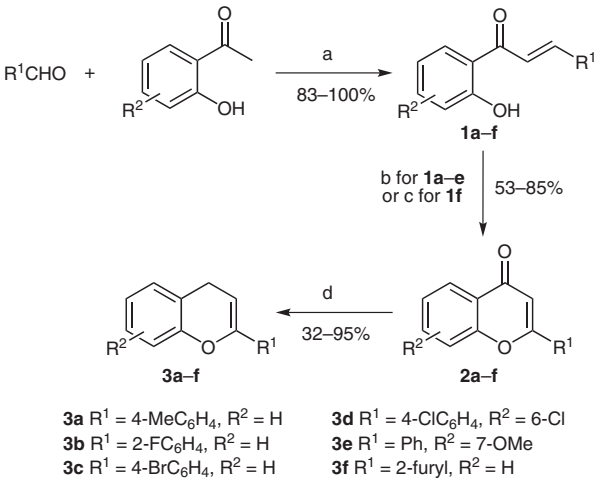


Figure 1

Despite the obvious interest in this class of compounds, only a few synthetic methods have been developed that give access to enantiomerically enriched chromanes, the main strategies being based on the Sharpless asymmetric epoxidation[4] or the Mitsunobu reaction.[5] In connection with our work on iridium-catalyzed asymmetric hydrogenation,[6] we thought that the enantioselective reduction of the enol ether unit of the corresponding chromenes would open up an attractive route to optically active chromanes.

Herein we report the successful realization of this strategy, which gives access to a variety of 2-monosubstitued chromanes in high enantiomeric purity.[7]

4*H*-Chromenes can be prepared by numerous synthetic routes starting from flavylium ions,[8] diketones,[9] chalcones[10] or other precursors. The general route that we used is shown in Scheme 1. Chalcones **1a–f**, obtained in high yields from inexpensive commercially available starting materials,[11] were readily converted to flavones **2a–e** by iodine-promoted ring closure using 1.2 equivalents of iodine.[10c] For the cyclization of the furyl-substituted derivative **1f** only a catalytic amount of iodine was used in order to avoid iodination of the furan ring.[12] Finally, reduction with $LiAlH_4$–$AlCl_3$[8a] led to the desired chromenes **3a–f** in good to moderate yields.[13]



Scheme 1 Synthesis of 4*H*-chromenes. *Reagents and conditions*: (a) KOH, EtOH, r.t., 14 h; (b) I_2 (1.2 equiv), triethylene glycol, 150 ºC, 4 h; (c) 1 crystal of I_2, DMSO, reflux, 10 min and then at r.t., 30 min; (d) $LiAlH_4$–$AlCl_3$, THF, 0 ºC, 30 min.

The cyclohexyl-substituted chromene **5** could not be synthesized by this route because the reduction of cyclohexylchromanone led to formation of decomposition products. Therefore, an alternative synthesis starting from dihydrocoumarin was undertaken (Scheme 2). Grignard reaction with cyclohexylmagnesium chloride followed by dehydration of the crude hemiacetal **4** after 48 hours afforded the cyclohexylchromene **5** in 23% overall yield.[14,15]

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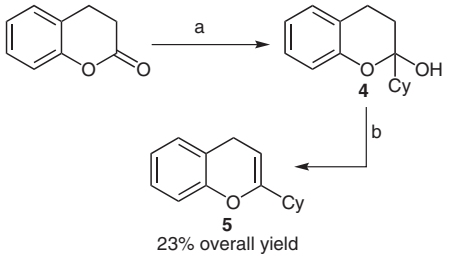


Scheme 2 Synthesis of 2-cyclohexylchromene **5**. *Reagents and conditions*: (a) CyMgCl (4 equiv), Et_2O, reflux, 48 h; (b) *p*-toluenesulfonic acid (cat.), toluene, reflux, 2 h.

2-Phenyl-4*H*-chromene (**6**) and 2-phenyl-4*H*-benzo[*h*]-chromene (**7**; Figure 2) were obtained by reduction of commercially available flavone and β-naphthoflavone, respectively, with $LiAlH_4$–$AlCl_3$.

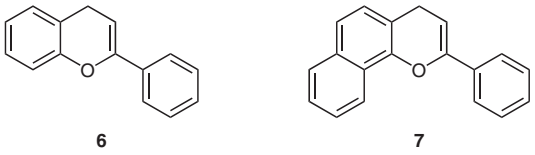


Figure 2 Flavenes prepared from commercially available flavones

With the various chromene derivatives in hand, the enantioselective hydrogenation of the enol ether double bond was studied, employing iridium complexes **8**–**10** as catalysts (Figure 3).[6a–6c]

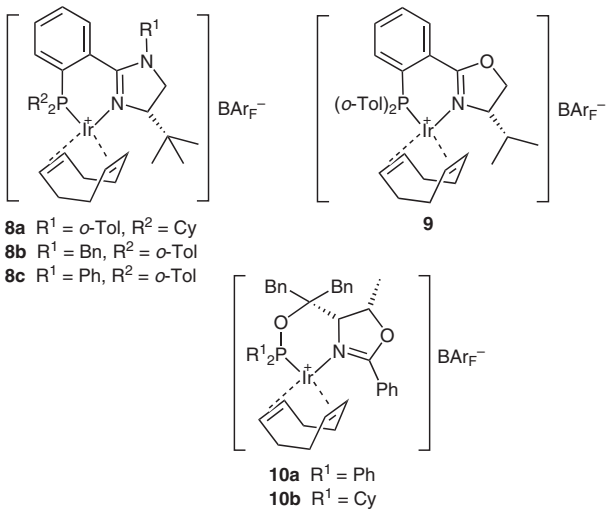
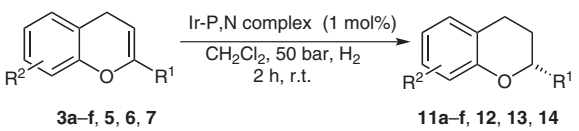


Figure 3 Iridium catalysts employed in chromene hydrogenation

The reactions were performed with 1 mol% of iridium complex in dichloromethane under 50 bar hydrogen pressure at room temperature in an autoclave (Equation 1).

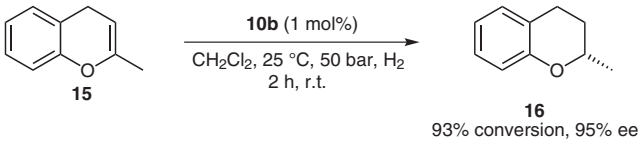


Equation 1 Asymmetric hydrogenation of chromenes

All substrates reacted cleanly under these conditions to afford the desired 2-substituted chromanes as the only detectable products (Tables 1 and 2).

Complexes **8a**–**c** derived from phosphinoimidazoline ligands gave low conversion in most cases and the enantioselectivities were moderate at best (Table 1). Higher conversions and better enantioselectivities were obtained with the Ir(PHOX) catalyst **9** and the corresponding complexes **10a**,**b** derived from threonine-derived ligands (ThrePHOX) (Table 2). Clearly the best results were achieved with complex **10b** bearing an electron-rich dicyclohexylphosphino group. This catalyst showed the highest reactivity and gave full conversion for all substrates except for **3c** and **3d**. Excellent enantioselectivities of >95% ee were obtained in all cases with the exception of the hydrogenation of the 4-bromophenyl-substituted chromene **3c**, which gave 91% ee.

Next we studied the hydrogenation of 2-methylchromene **15**,[16] prepared by cyclization of 4-(2-hydroxyphenyl)butan-2-one followed by dehydration.[17] Again, high conversion and excellent enantioselectivity, were obtained under standard conditions (Equation 2). This substrate had been hydrogenated before using a Ru-BINAP complex (1 mol%, 100 bar H_2, 50 ºC, >24 h). Although full conversion was observed under these rather forcing conditions, the enantiomeric excess was only 64%.[18]



Equation 2 Asymmetric hydrogenation of methylchromene **17**

We also attempted the synthesis of the tephrowatsin E, by asymmetric hydrogenation of the corresponding flavene, which was obtained from commercially available 5,7-dihydroxyflavone by methylation of the hydroxyl groups and subsequent reduction. When 2 mol% of catalyst **10b** was used 97% conversion was obtained in four hours, but surprisingly the ee was only 5%.

A chromene derivative with a tetrasubstituted C=C bond, 3-methyl-2-phenyl-4*H*-chromene, was also tested. However, no reaction was observed in this case under a range of reaction conditions.[19] Other catalysts, derived from pyridine-based ligands,[6b,c] were examined, but again, gave no hydrogenation.

Finally, 2-phenyl-4*H*-thiochromene (**17**),[14] which was prepared by reduction of commercially available 2-phenyl-4*H*-thiochromen-4-one with $LiAlH_4$–$AlCl_3$, was examined as substrate (Equation 3). Under standard conditions conversion was low (15%), but the enantioselectivity was very high (99% ee). Higher catalyst loading of 2 mol% and a reaction time of 24 hours led to 54%, conversion, while the ee remained at 99%. When the reaction was performed at 40 ºC the conversion reached 73%, but the enantioselectivity decreased to 91% ee.

Table 1 Asymmetric Hydrogenation of Chromenes using Iridium Complexes **8a–c**[a]

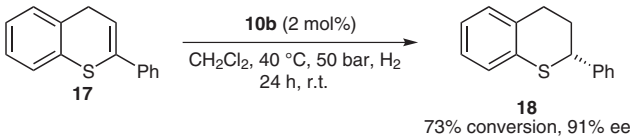
			Catalysts					
			8a		**8b**		**8c**	
Entry	Substrates	Products	Conversion (%)[b]	ee (%)[c]	Conversion (%)[b]	ee (%)[c]	Conversion (%)[b]	ee (%)[c]
1	**3a**	**11a**	50	84	53	44	44	58
2	**3b**	**11b**	2	–[d]	15	60	23	75
3	**3c**	**11c**	6	34	26	40	38	50
4	**3d**	**11d**	11	52	26	45	47	69
5	**3e**	**11e**	10	63	40	28	37	48
6	**3f**	**11f**	9	72	21	50	32	60
7	**5**	**12**	75	20	>99	35	>99	69
8	**6**	**13**	–[e]	–[e]	42	35	75	53
9	**7**	**14**	25	70	60	26	73	35

[a] Reaction conditions: see general procedure in experimental section.
[b] Determined by GC analysis.
[c] Determined by HPLC analysis (CHIRACEL OD-H).
[d] Not determined.
[e] Not tested.

Table 2 Asymmetric Hydrogenation of Chromenes using Iridium Complexes **9** and **10a**,**b**[a]

			Catalysts					
			9		**10a**		**10b**	
Entry	Substrates	Products	Conversion (%)[b]	ee (%)[c]	Conversion (%)[b]	ee (%)[c]	Conversion (%)[b]	ee (%)[c]
1	**3a**	**11a**	97	75	77	86	>99	98
2	**3b**	**11b**	67	69	77	93	>99	>99
3	**3c**	**11c**	61	60	42	80	95	91
4	**3d**	**11d**	77	79	32	81	90	97
5	**3e**	**11e**	49	70	32	70	>99	>99
6	**3f**	**11f**	93	63	76	90	>99	97
7	**5**	**12**	>99	50	>99	93	>99	95
8	**6**	**13**	99	72	74	80	>99	99
9	**7**	**14**	>99	58	91	82	>99	96

[a] Reaction conditions: see general procedure in experimental section.
[b] Determined by GC analysis.
[c] Determined by HPLC analysis (CHIRACEL OD-H).



Equation 3 Asymmetric hydrogenation of thioflavene

The absolute configuration of the hydrogenation products was assigned by comparison of the optical rotation of the products **13**, enantioenriched BW683C (**11d**) and **16** with literature values.[5,18,20]

In summary, iridium-catalyzed asymmetric hydrogenation[21] of 2-substituted chromenes provides an efficient, highly enantioselective route to chiral chromanes. A variety of differently substituted products, including flavanes which are of interest because of their biological activity, can be readily prepared in this way.

Acknowledgment

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(13) The chromenes were fully characterized. For the known compounds, the spectroscopic and physical data are in agreement with those previously reported in literature. These chromenes are generally air and temperature sensitive, and therefore should be stored under argon at –20 ºC to avoid decomposition.
Representative example:
2-(4-Bromophenyl)-4*H*-chromene (3c): The product was isolated after flash chromatography on silica gel (pentane–EtOAc, 99:1) as a white solid in 95% yield; mp 105 ºC; R_f 0.42 (pentane–EtOAc, 9:1). IR (KBr): 3043, 2830, 1667, 1583, 1488, 1239 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 3.12 (δ, *J* = 3.9 Hz, 2 H), 4.99 (t, *J* = 3.9 Hz, 1 H), 6.78 (m, 1 H), 6.84 (m, 1 H), 6.97 (m, 2 H), 7.26–7.29 (m, 4 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 24.5, 97.2, 117.0, 119.7, 122.5, 123.7, 126.5, 128.0, 129.2, 131.7, 133.8, 148.4, 152.2. MS (EI): *m*/*z* (%) = 226.2 (66.3) [M^+], 225.1 (100), 131.1 (19.3). Anal. Calcd for $C_{15}H_{11}OBr$: C, 62.74; H, 3.86. Found: C, 62.79; H, 3.85.

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(15) **2-Cyclohexyl-4*H*-chromene (5)**: The product was isolated after flash chromatography on silica gel (100% pentane) as a pale yellow oil (23% yield); R_f 0.75 (pentane–EtOAc, 9:1). IR (neat): 3026, 2926, 1693, 1586, 1488, 1235 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 1.06–1.22 (m, 3 H), 1.33 (m, 2 H), 1.57 (m, 1 H), 1.68 (m, 2 H), 1.94 (m, 2 H), 2.04 (m, 1 H), 3.17 (d, *J* = 3.5 Hz, 2 H), 4.49 (br dt, *J* = 0.7, 3.5 Hz, 1 H), 6.78–6.83 (m, 2 H), 6.92–6.95 (m, 2 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 24.2, 26.6, 26.7, 30.9, 42.2, 93.2, 116.7, 120.5, 123.1, 127.6, 129.3, 152.9, 156.3. MS (EI): *m*/*z* (%) = 214.2 (18.2) [M^+], 213.3 (21.3), 131.1 (100). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.83; H, 8.60.

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(17) **2-Methyl-4*H*-chromene (15)**: Salicylaldehyde (0.53 mL, 5 mmol) was added to a solution of DL-proline (99 mg, 20 mol%) and acetone (7.4 mL, 20 equiv) in DMF–H_2O (1:1, 20 mL). The mixture was heated for 48 h at 90 ºC. The mixture was cooled to r.t., extracted with EtOAc (2 ×) and washed with brine (4 ×), affording, after removal of the organic solvent, the corresponding hydroxy chalcone as an orange solid. The crude product was dissolved in EtOH (5 mL) and hydrogenated under 1 bar H_2 pressure using Raney-Ni as catalyst. The reaction was monitored by GC (Machary-Nagel, Optima Amin-5 column). When the reaction was complete, the solution was filtered through celite, extracted with Et_2O (2 ×) and washed with brine (2 ×). The organic layer was concentrated under reduced pressure to give the corresponding hydroxy ketone, which, without purification, was refluxed in toluene (10 mL) with a catalytic amount of *p*-toluenesulfonic acid (100 mg) and 4 Å molecular sieves (2 g) for 2 h. After this time, the mixture was cooled to r.t., filtered, washed with sat. aq $NaHCO_3$ solution, and brine. The organic solvent was then removed and the crude product was purified by flash chromatography to give the pure **15** in 29% yield as colorless oil.

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(19) The reaction failed even at high catalyst loadings of up to 4 mol%, 100 bar hydrogen pressure, and with long reaction times.

(20) For other products the absolute configuration was assumed to be the same because the same catalysts were used in the hydrogenation.

(21) **Typical Procedure for the Catalytic Asymmetric Hydrogenation of Chromenes**: A solution of chromene (0.5 mmol) and iridium complex **10b** (8.7 mg, 5 μmol, 1 mol%) in anhyd dichloromethane (2.5 mL, Fluka anhyd solvents grade) under an argon atmosphere was placed in an autoclave, which was sealed, pressurized (50 bar hydrogen gas) and stirred at r.t. for 2 h. The solvent was evaporated and the catalyst was removed by filtration through a short silica gel column (3 × 1 cm) with a mixture of pentane and ethyl acetate (1:1) as eluent to give the desired chromane after evaporation of the solvent.
For catalyst screening, reactions were carried out on a 0.1-mmol scale.
Analytical data for new compounds are given below. For known compounds, the observed spectra were in agreement with the reported data.[5,18] For products which were reported in the literature as racemates, only $[\alpha]_D$, ^{1}H, ^{13}C NMR and HPLC data are listed.
(*R*)-2-(2-Fluorophenyl)chromane (11b): $[\alpha]_D^{20}$ +28.9 (*c* = 0.5, $CHCl_3$; >99% ee); R_f 0.82 (pentane–EtOAc, 9:1). IR (KBr): 2929, 1582, 1488, 1234 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (m, 1 H), 2.26 (m, 1 H), 2.79 (ddd, *J* = 3.8, 4.8, 16.5 Hz, 1 H), 3.03 (ddd, *J* = 5.8, 11.4, 16.5 Hz, 1 H), 5.40 (dd, *J* = 2.2, 10.1 Hz, 1 H), 6.88 (m, 2 H), 7.05–7.20 (m, 4 H), 7.30 (m, 1 H), 7.55 (dt, *J* = 1.5, 7.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 29.3, 72.2 (d, *J* = 3.5 Hz), 115.7 (d, *J* = 21.5 Hz), 117.3, 120.9, 122.2, 124.7 (d, *J* = 3.5 Hz), 127.8 (d, *J* = 3.8 Hz), 127.9, 129.4 (d, *J* = 12.6 Hz), 129.5 (d, *J* = 8.4 Hz), 130.0, 158.7, 160.0 (d, *J* = 276.3 Hz). MS (EI): *m*/*z* (%) = 228.2 (100) [M$^+$], 119.1 (46.4). Anal. Calcd for $C_{15}H_{13}FO$: C, 78.93; H, 5.74. Found: C, 78.65; H, 5.93. HPLC: Chiracel OD-H, 100% heptane, 20 ºC, flow rate: 0.5 mL/min, $t_R(R)$ = 27.6 min, $t_R(S)$ = 29.6 min.
(*R*)-2-(4-Bromophenyl)chromane (11c): $[\alpha]_D^{20}$ +22.4 (*c* = 0.5, $CHCl_3$; 91% ee, 95% conversion); mp 85 ºC; R_f 0.80 (pentane–EtOAc, 9:1). IR (KBr): 2926, 1579, 1487, 1235 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (m, 1 H), 2.20 (m, 1 H), 2.79 (br ddd, *J* = 3.9, 5.0, 16.7 Hz, 1 H), 2.99 (ddd, *J* = 5.8, 11.4, 16.7 Hz, 1 H), 5.03 (dd, *J* = 2.5, 10.1 Hz, 1 H), 6.87–6.91 (m, 2 H), 7.06–7.15 (m, 2 H), 7.31 (m, 2 H), 7.51 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 30.3, 77.6, 117.3, 120.9, 122.0, 122.1, 127.8, 128.1, 130.0, 132.0, 141.2, 155.2. MS (EI): *m*/*z* (%) = 290.1 (76.2) [M$^+$], 289.1 (15.8), 209.1 (100). Anal. Calcd for $C_{15}H_{13}OBr$: C, 62.30; H, 4.53. Found: C, 62.27; H, 4.49. HPLC: Chiracel OD-H, heptane–2-propanol, 99.5/0.5, 20 ºC, flow rate: 0.5 mL/min, $t_R(S)$ = 18.0 min, $t_R(R)$ = 20.6 min.
(*R*)-7-Methoxy-2-phenylchromane(11e): $[\alpha]_D^{20}$ +26.7 (*c* = 1.0, $CHCl_3$; >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (m, 1 H), 2.26 (m, 1 H), 2.76 (m, 1 H), 2.94 (m, 1 H), 3.77 (s, 3 H), 5.40 (dd, *J* = 2.2, 10.1 Hz, 1 H), 6.49 (m, 2 H), 6.96 (br d, *J* = 7.2 Hz, 1 H), 7.31–7.34 (m, 1 H), 7.38–7.41 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 30.6, 55.0, 78.0, 102.2, 108.2, 114.2, 126.5, 128.2, 128.7, 130.4, 142.6, 156.7, 160.1. HPLC: Chiracel OD-H, 100% heptane, 20 ºC, flow rate: 0.5 mL/min, $t_R(R)$ = 49.2 min, $t_R(S)$ = 54.6 min.
(*R*)-2-(2-Furanyl)chromane (11f): $[\alpha]_D^{20}$ –4.7 (*c* = 0.9, $CHCl_3$; 97% ee); mp 50 ºC; R_f 0.85 (pentane–EtOAc, 9:1). IR (KBr): 2932, 1562, 1456, 1232 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 1.84 (m, 1 H), 2.07 (m, 1 H), 2.48 (m, 2 H), 4.92 (dd, *J* = 2.5, 9.8 Hz, 1 H), 6.14 (dd, *J* = 1.8, 3.3 Hz, 1 H), 6.24 (d, *J* = 3.3 Hz, 1 H), 6.87 (br dt, *J* = 1.5, 7.1 Hz, 1 H), 6.94 (d, *J* = 7.1 Hz, 1 H), 7.04–7.10 (m, 2 H), 7.15 (d, *J* = 1.0 Hz, 1 H). ^{13}C NMR (100 MHz, C_6D_6): δ = 24.7, 26.4, 71.5, 107.5, 110.6, 117.5, 120.9, 121.9, 128.1, 129.9, 142.4, 154.7, 155.3. MS (EI): *m*/*z* (%) = 240.2 (100) [M$^+$], 136.1 (20.5). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.11; H, 5.99. HPLC: Chiracel OD-H, 100% heptane, 20 ºC, flow rate: 0.5 mL/min, $t_R(R)$ = 27.9 min, $t_R(S)$ = 31.4 min.
(*R*)-2-Cyclohexylchromane (12): $[\alpha]_D^{20}$ –62.1 (*c* = 1.0, $CHCl_3$; 95% ee); R_f 0.88 (pentane–EtOAc, 9:1). IR (neat): 2925, 1582, 1488, 1236 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.43 (m, 6 H), 1.55–1.80 (m, 5 H), 1.94–2.00 (m, 2 H), 2.70–2.85 (m, 2 H), 3.73 (ddd, *J* = 2.8, 5.9, 9.8 Hz, 1 H), 6.88 (br ddd, *J* = 1.7, 7.4, 8.6 Hz, 1 H), 7.02 (d, *J* = 7.3 Hz, 1 H), 7.05–7.12 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 25.5, 26.7, 28.8, 30.2, 42.5, 80.3, 117.4, 120.3, 122.6, 127.7, 129.9, 156.2. MS (EI): *m*/*z* (%) = 216.2 (29.5) [M$^+$], 120.1 (100). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.01; H, 9.33. HPLC: Chiracel OD-H, 100% heptane, 15 ºC, flow rate: 0.5 mL/min, $t_R(S)$ = 18.6 min, $t_R(R)$ = 19.9 min.
(*R*)-2-Phenyl-3,4-dihydro-2*H*-benzo[*h*]chromene (14): $[\alpha]_D^{20}$ +139.5 (*c* = 0.6, $CHCl_3$; 96% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (m, 1 H), 2.34 (m, 1 H), 2.88 (m, 1 H), 3.13 (m, 1 H), 5.25 (dd, *J* = 2.3, 9.9 Hz, 1 H), 7.18 (d, *J* = 8.3 Hz, 1 H), 7.33–7.46 (m, 6 H), 7.51 (d, *J* = 7.4 Hz, 2 H), 7.76 (m, 1 H), 8.25 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.3, 30.2, 77.9, 115.8, 120.2, 122.2, 125.6, 126.1, 126.3, 127.0, 127.9, 128.0, 128.7, 128.8, 134.0, 142.5, 150.3. HPLC: Chiracel OD-H, heptane–2-propanol, 98:2, 20 ºC, flow rate: 0.5 mL/min, $t_R(R)$ = 11.4 min, $t_R(S)$ = 13.2 min.
(*R*)-2-Phenylthiochromane (18): $[\alpha]_D^{20}$ –98.5 (*c* = 0.4, $CHCl_3$; 91% ee, 73% conversion); mp 53 ºC; R_f = 0.48 (pentane). IR (KBr): 2932, 1452, 1436 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19–2.28 (m, 1 H), 2.38–2.44 (m, 1 H), 2.95 (m, 2 H), 4.45 (dd, *J* = 3.3, 7.6 Hz, 1 H), 6.99 (m, 1 H), 7.06–7.12 (m, 3 H), 7.29 (m, 1 H), 7.30–7.36 (m, 2 H), 7.41 (dd, *J* = 1.3, 8.1 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.0, 31.1, 46.3, 124.0, 125.9, 126.5, 127.6, 127.7, 128.6, 129.8, 133.0, 134.0, 141.9. Anal. Calcd for $C_{15}H_{14}S$: C, 79.60; H, 6.23. Found: C, 79.29; H, 6.47. HPLC: Chiracel OD-H, heptane–2-propanol, 80:20, 20 ºC, flow rate: 0.5 mL/min, $t_R(R)$ = 10.1 min, $t_R(S)$ = 11.3 min.