Synthesis of Chromanes and 4*H*-Chromenes: Exploring the Oxidation of 2*H*-Chromenes and Dihydro-1-benzoxepines by Hypervalent Iodine(III)

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Abstract: The reaction of various oxygen-containing benzo-fused cycloalkenes were studied with the hypervalent iodine reagent hydroxy(tosyloxy)iodo]benzene [PhI(OH)OTs, HTIB]. 2*H*-Chromene and 4-methyl-2*H*-chromene resulted in substituted 4*H*-chromene and *cis*-3,4-dialkoxy-4-methyl-3,4-dihydro-2*H*-chromenes, respectively. Ring contraction to chromanes and benzofurans was observed for dihydrobenzoxepines and 2,2-dimethyl-2*H*-chromenes, respectively.

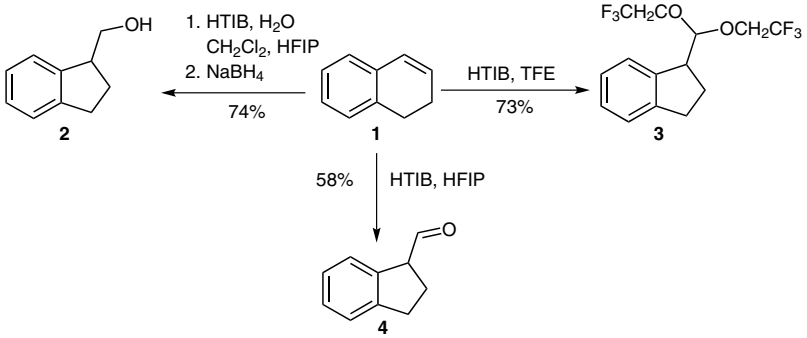
Key words: chromenes, chromanes, Koser's reagent, ring contraction, hypervalent iodine

Benzopyrans, such as chromanes[1] and chromenes,[2] occur in many biologically active compounds, and are key intermediates in the construction of numerous natural products and biologically active agents. Thus, several strategies have been developed for their synthesis.[3]

In recent years, owing to their ecofriendly nature and unique reactivity, hypervalent iodine compounds have emerged as versatile and attractive reagents for a number of noteworthy metal-free transformations.[4] [Hydroxy(tosyloxy)iodo]benzene or Koser's reagent [PhI(OH)OTs, HTIB][5] is a significant member of the family of hypervalent iodine reagents, because of its extensive synthetic applications that cover areas such as tosyloxylation,[6] intramolecular oxygenations,[7] hydroxylation,[8] oxidative rearrangements[9] and oxidative biaryl coupling.[10] We have developed the hydroxy(tosyloxy)iodo]benzene-mediated ring contraction of 1,2-dihydronaphthalenes into indanes (Scheme 1).[11–13] This rearrangement was applied in the diastereoselective total synthesis of (+)-mutisianthol[14] and (±)-indatraline.[12,15] This encouraged us to examine the behavior of 2*H*-chromenes and related cyclic alkenes with hydroxy(tosyloxy)iodo]benzene, resulting in new methods for the synthesis of different oxygen-containing heterocycles, such as 4*H*-chromenes, chromanes, and benzofurans. These reactions proceed under mild conditions, they are easily performed, and they do not pose major toxicity problems.

We focused our initial efforts on 2*H*-chromene (**5a**) which was easily prepared in high yield from commercially available chroman-4-one.[11,16] Based on our previous experience,[11,12,14,15,17] hydroxy(tosyloxy)iodo]benzene was selected from among several available hypervalent iodine(III) reagents. The reactions of **5a** were carried out with varying solvents, methanol, trimethyl orthoformate (TMOF), triethyl orthoformate (TEOF), acetonitrile, 2,2,2-trifluoroethanol (TFE), hexafluoropropan-2-ol (HFIP), and dichloromethane, and temperatures.[18] The most significant tests are shown in Table 1. The reaction in methanol or trimethyl orthoformate gave methoxy-substituted 4*H*-chromene **6a** as the main product, together with the *trans*-addition product **7a** (entries 1 and 2). The reaction in triethyl orthoformate gave a similar result (entry 3). The reaction carried out in 2,2,2-trifluoroethanol led to 2,2,2-trifluoroethoxy-substituted 4*H*-chromene **10a** in 24% yield; conversely, the addition product was not isolated (entry 4).

The formation of **6a** can be explained by the mechanism shown in Scheme 2.[9,11,19] The first step is electrophilic attack by iodine(III) on the double bond, forming the cyclic organoiodine **20**. This intermediate is then attacked by the



Scheme 1 Iodine(III)-mediated ring contraction of 1,2-dihydronaphthalene

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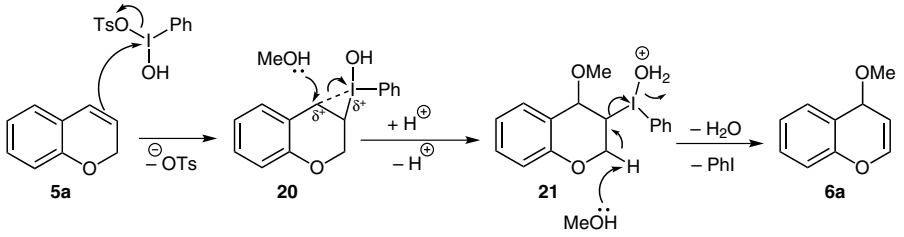


Scheme 2 Mechanism for the formation 4*H*-chromene

nucleophilic solvent at the benzylic carbon to form **21**. The final step is the β-elimination, displacing PhI and water to give substituted 4*H*-chromene **6a**.

Considering that the less electronegative sulfur atom could have a less pronounced effect on the course of reaction in comparison to the oxygen atom, the behavior of 2*H*-thiochromene (**5b**) was investigated. However, the reaction of **5b** with hydroxy(tosyloxy)iodo]benzene in triethyl orthoformate led to 4*H*-thiochromene **8b**, similarly to chromene **5a** (entry 5).[20]

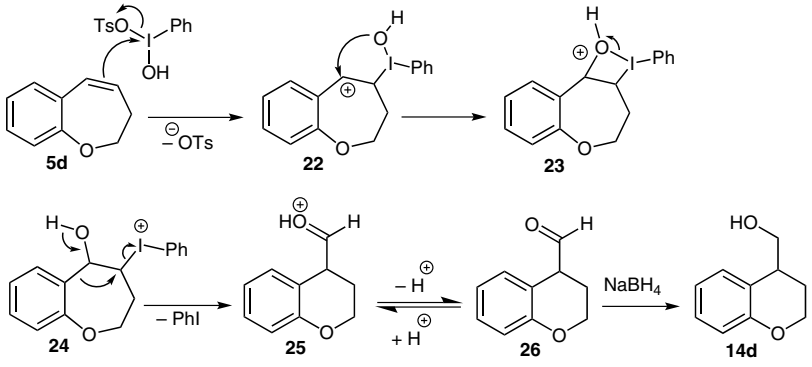
Taking into account that alkyl-substituted alkenes have different behavior when compared to unsubstituted alkenes,[12,21] the reaction of chromene **5c** was also performed under several conditions. The treatment of **5c** with hydroxy(tosyloxy)iodo]benzene in methanol or trimethyl orthoformate gave *cis*-dimethoxychromane **11c** in a diastereoselective fashion and in good yield (entries 6 and 7). The relative configuration was assigned by NMR including NOESY experiments. Analogously, the reaction of **5c** in triethyl orthoformate gave **12c** (entry 8). The fluorinated solvent 2,2,2-trifluoroethanol was also tested without success. The diastereoselective synthesis of *cis*-dimethoxychromanes presumably follows a mechanism similar to the formation of *cis*-addition product from 1,2-dihydronaphthalenes.[11,12]

Based on the facilitating effect of the oxygen atom in the β-elimination (Scheme 2), the oxidation of the substrates **5d**–**g**, on which this effect would be less significant, was investigated.

In the seven-membered-ring substrates **5d** and **5e**, the possibility of β-elimination could be avoid due to the presence of an additional methylene carbon. When the alkene **5d** was treated with hydroxy(tosyloxy)iodo]benzene in 2,2,2-trifluoroethanol, the ring contraction product **13d** was obtained in good yield (entry 9). Using the mixed solvent system hexafluoropropan-2-ol–dichloromethane followed by in situ reduction with sodium borohydride led to the hydroxy functionalized chromane **14d** in excellent yield (entry 10). In this case the addition of small amount of water is necessary to decrease the formation of undesired acetal product **15d**. The methyloxepine **5e** also undergoes ring contraction providing the keto-substituted chromane **16e** in good yield (entry 11).

Several reaction conditions were tested for 2,2-dimethyl-2*H*-chromene (**5f**). In this case, we expected the ring contraction product as there is no hydrogen atom at the carbinolic carbon, which is responsible for the formation of substituted 4*H*-chromene, such as **6a**. Ring-contraction products, such as the benzofurans **17f** and **18f**, were indeed isolated, however, in low yield (entries 12 and 13). Intense efforts were made to improve these yields, but without success.[22] Analogues results were observed for 2,2,4-trimethyl-2*H*-chromene (**5g**) (entries 14 and 15).[23]

The mechanism for the ring contraction of **5d** in hexafluoropropan-2-ol–dichloromethane is shown in Scheme 3.[11–13] The electrophilic attack of hydroxy(tosyloxy)iodo]benzene on the double bond gave carbocation **22**. The oxygen lone pair attacks at the benzylic carbon resulting in the cyclic oxonium ion **23**. Ring opening of the four-membered ring gives iodonium intermediate **24**. The migration of an aryl bond on **24** leads to the ring-contraction intermediate **25**. After proton transfer, aldehyde **26** is reduced to the isolated alcohol **14d**. The ring-contraction reactions under other conditions (entries 9, 11–15) take place by similar mechanisms.



Scheme 3 Mechanism for the ring contraction in hexafluoropropan-2-ol–dichloromethane

Table 1 Reaction of Oxygen-Containing Benzo-Fused Cyclic Alkenes **5a**–**g** with [Hydroxy(tosyloxy)iodo]benzene (1.1 equiv)[18,20,22,23]

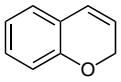
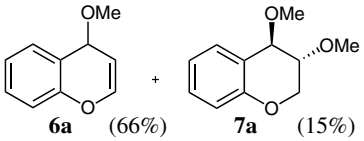
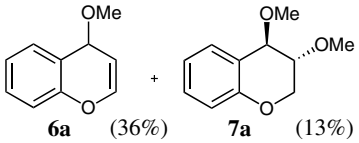
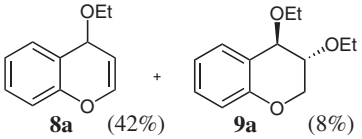
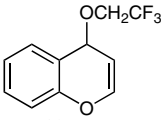
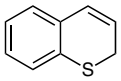
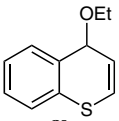
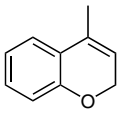
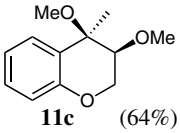
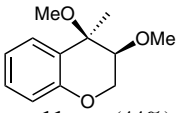
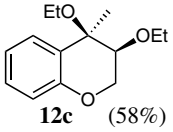
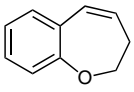
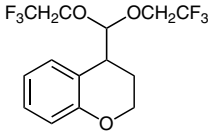
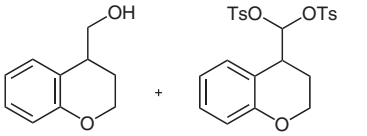
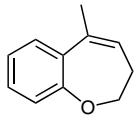
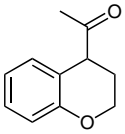
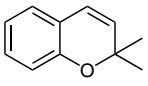
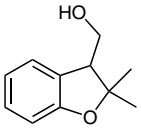
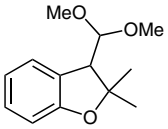
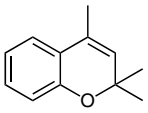
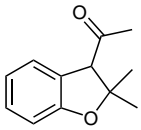
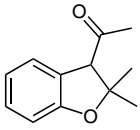
Entry	Substrate	Condition	Product (yield[a])
1	 **5a**	MeOH, 0 °C, 3 h	 **6a** (66%) + **7a** (15%)
2	**5a**	TMOF, 0 °C, 2 h	 **6a** (36%) + **7a** (13%)
3	**5a**	TEOF, r.t., 4 h	 **8a** (42%) + **9a** (8%)
4	**5a**	TFE, 0 °C, 2 h	 **10a** (24%)
5	 **5b**	TEOF, 0 °C, 30 min	 **8b** (60%)
6	 **5c**	MeOH, 0 °C, 1 h	 **11c** (64%)
7	**5c**	TMOF, 0 °C, 2 h	 **11c** (44%)
8	**5c**	TEOF, r.t., 4 h	 **12c** (58%)
9	 **5d**	TFE, 0 °C, 30 min	 **13d** (50%)
10	**5d**	1. HFIP–CH_2Cl_2 (1:4), H_2O (22 equiv). 2. $NaBH_4$, 2 h	 **14d** (87%) + **15d** (9%)

Table 1 Reaction of Oxygen-Containing Benzo-Fused Cyclic Alkenes **5a–g** with [Hydroxy(tosyloxy)iodo]benzene (1.1 equiv)[18,20,22,23] (continued)

Entry	Substrate	Condition	Product (yield[a])
11	 **5e**	TFE, 0 °C, 30 min	 **16e** (58%)
12	 **5f**	1. HFIP–CH_2Cl_2 (1:4), H_2O (22 equiv) 2. $NaBH_4$, 2 h	 **17f** (31%)
13	**5f**	MeOH, 0 °C, 2 h	 **18f** (30%)
14	 **5g**	MeOH, 0 °C, 1 h	 **19g** (24%)
15	**5g**	MeOH–Et_2O, 0 °C, 1 h	 **19g** (24%)

[a] Isolated yield after purification by column chromatography.

In conclusion, the behavior of 2*H*-chromenes and 2,3-dihydro-1-benzoxepine with hydroxy(tosyloxy)iodo]benzene was explored. This study provides new approaches to give a variety of different O-heterocycles in moderate to good yield. This methodology is mild and environmentally friendly.

All commercially available reagents were used without further purification unless otherwise noted. All solvents used for reactions and chromatography were dried and purified by standard methods. TLC analyses were performed using silica gel 60F 254 precoated plates, with detection by UV absorption (254 nm) and by spraying with *p*-anisaldehyde and phosphomolybdic acid solns followed by charring at ~150 °C for visualization. Flash column chromatography was performed using silica gel 200–400 mesh. All NMR analyses were recorded using $CDCl_3$ as solvent and TMS as internal standard with reference to internal solvent. Preparation of substrates **5a**,[16] **5b**,[11] **5c**,[11] **5d**,[16,24] **5e**,[11,24] **5f**,[16,25] and **5g**[11,25] was performed as described in the literature.

4-Methoxy-4*H*-chromene (6a) and *trans*-3,4-Dimethoxy-3,4-dihydro-2*H*-chromene (7a); Typical Procedure 1

To a stirred soln of 2*H*-chromene (**5a**; 0.135 g, 1.02 mmol) in MeOH (5 mL) was added HTIB (0.450 g, 1.15 mmol) at 0 °C. This mixture was stirred for 3 h (TLC monitoring) and the reaction was quenched with sat. $NaHCO_3$ soln. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine (2 × 15 mL) and dried (anhyd $MgSO_4$). The crude product was purified by flash column chromatography (2% EtOAc–hexane) giving **6a** (0.106 g, 0.654 mmol, 66%) as a colorless oil and **7a** (0.029 g, 0.15 mmol, 15%) as a light yellowish oil.

4-Methoxy-4*H*-chromene (6a)

IR (film): 3052, 2956, 2927, 2829, 1729, 1643, 1607, 1575, 1489, 1458, 1087, 1034 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.49 (s, 3 H), 5.58 (d, *J* = 3.6 Hz, 1 H), 5.86 (dd, *J* = 9.6, 3.6 Hz, 1 H), 6.73 (d, *J* = 9.8 Hz, 1 H), 6.91–7.01 (m, 2 H), 7.10–7.25 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.0, 95.8, 116.5, 119.6, 120.7, 121.5, 126.6, 127.0, 129.3, 151.3.

LRMS: *m*/*z* (%) = 162 ($M^{+\bullet}$, 23), 161 (21), 146 (4), 131 (100), 118 (5), 103 (11). 91 (15), 77 (21), 65 (8), 51 (13), 32 (20).

HRMS [ESI(+)]: *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{10}O_2Na$: 185.0573; found: 185.0583.

***trans*-3,4-Dimethoxy-3,4-dihydro-2*H*-chromene (7a)**

IR (film): 3074, 3042, 2983, 2931, 2892, 2825, 1698, 1609, 1585, 1489, 1463 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.46 (s, 3 H), 3.47 (s, 3 H), 3.66 (td, *J* = 3.3, 1.8 Hz, 1 H), 4.18 (dd, *J* = 12, 1.8 Hz, 1 H), 4.19 (dd, *J* = 3.6, 1.5 Hz, 1 H), 4.33 (ddd, *J* = 11.7, 3.3, 1.5 Hz, 1 H), 6.85–6.89 (m, 1 H), 6.92 (dd, *J* = 7.5, 1.2 Hz, 1 H), 7.18–7.25 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.5, 56.9, 62.8, 73.9 (2 C), 116.8, 119.4, 120.3, 129.8, 131.4, 154.1.

LRMS: *m*/*z* (%) = 194 ($M^{+\bullet}$, 13), 162 (9), 136 (53), 121 (41), 107 (100), 91 (13), 77 (19), 65 (11), 51 (10).

HRMS [ESI(+)]: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}O_3Na$: 217.0835; found: 217.0832.

4-Ethoxy-4*H*-chromene (8a) and *trans*-3,4-Diethoxy-3,4-dihydro-2*H*-chromene (9a); Typical Procedure 2

HTIB (0.450 g, 1.14 mmol) was added at r.t. to a stirred soln of 2*H*-chromene (**5a**; 0.135 g, 1.02 mmol) in TEOF (6 mL). The resulting turbid soln became clear after 10 min. After 4 h, the reaction was quenched with sat. $NaHCO_3$ soln. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine soln (2 × 20 mL) and dried (anhyd $MgSO_4$). The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (5% EtOAc–hexane) giving product **8a** (0.075 g, 0.42 mmol, 42%) as a colorless oil and **9a** (0.018 g, 0.081 mmol, 8%) as a light yellowish oil.

4-Ethoxy-4*H*-chromene (8a)

IR (film): 3046, 2976, 2927, 2880, 1718, 1644, 1607, 1576, 1497 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7 Hz, 3 H), 3.65 (dq, *J* = 9.7, 7 Hz, 1 H), 3.64 (dq, *J* = 9.7, 7 Hz, 1 H), 5.68 (d, *J* = 3.8 Hz, 1 H), 5.85 (dd, *J* = 9.6, 3.8 Hz, 1 H), 6.71 (d, *J* = 9.6 Hz, 1 H), 6.96 (d, *J* = 7.2 Hz, 2 H), 7.10–7.24 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.2, 63.4, 94.8, 116.5, 119.9, 120.7, 121.4, 126.5, 127.0, 129.2, 151.4.

LRMS: *m*/*z* (%) = 176 ($M^{+\bullet}$, 42), 147 (35), 131 (100), 118 (5), 103 (25), 91 (36), 77 (32), 65 (18), 51 (23), 39 (22).

HRMS [ESI(+)]: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}O_2Na$: 199.0725; found: 199.0715.

***trans*-3,4-Diethoxy-3,4-dihydro-2*H*-chromene (9a)**

IR (film): 3042, 2976, 2926, 2882, 1624, 1610, 1586, 1489, 1464 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 6.9 Hz, 3 H), 1.24 (t, *J* = 6.9 Hz, 3 H), 3.59–3.69 (m, 2 H), 3.69–3.76 (m, 3 H), 4.20 (dd, *J* = 11.7, 2.4 Hz, 1 H), 4.23–4.29 (m, 2 H), 6.85 (dd, *J* = 8.1, 1.2 Hz, 1 H), 6.91 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.19 (m, 1 H), 7.25 (dd, *J* = 7.5, 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 15.6, 64.0, 64.7, 64.8, 73.0, 73.2, 116.7, 120.4, 120.5, 129.4, 131.0, 154.1.

LRMS: *m*/*z* (%) = 222 ($M^{+\bullet}$, 6), 176 (9), 150 (42), 131 (16), 122 (71), 121 (100), 107 (30), 91 (28), 71 (26), 65 (13), 51 (10), 43 (22), 32 (29).

HRMS [ESI(+)]: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}O_3Na$: 245.1148; found: 245.1152.

4-(2,2,2-Trifluoroethoxy)-4*H*-chromene (10a); Typical Procedure 3

To a soln of 2*H*-chromene (**5a**; 0.142 g, 1.07 mmol) in TFE (6 mL) was added HTIB (0.462 g, 1.18 mmol) at 0 °C. Immediately after the addition of HTIB, the mixture became dark in color. After 2 h, the reaction was quenched with sat. $NaHCO_3$ soln. The mixture was extracted with EtOAc (3 × 10 mL), and the combined extracts were washed with brine soln (2 × 20 mL) and dried (anhyd $MgSO_4$). The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (2% EtOAc–hexanes) giving **10a** (0.590 g, 0.260 mmol, 24%) as a colorless oil.

IR (film): 3048, 2927, 2855, 1644, 1610, 1584, 1489 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.02 (dq, *J* = 12.6, 3.9 Hz, 1 H), 4.08 (dq, *J* = 12.3, 3.9 Hz, 1 H), 5.81 (d, *J* = 3.9 Hz, 1 H), 5.88 (dd, *J* = 9.6, 3.6 Hz, 1 H), 6.80 (d, *J* = 9.3 Hz, 1 H), 6.70–7.01 (m, 2 H), 7.14–7.17 (m, 1 H), 7.21–7.27 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.0 (q, *J* = 138 Hz, *C*H_2CF_3), 95.16, 116.5, 118.4, 120.3, 122.1, 123.7 (q, *J* = 1106.4 Hz, CH_2CF_3), 127.2, 127.6, 129.7, 150.6.

LRMS: *m*/*z* (%) = 230 ($M^{+\bullet}$, 9), 131 (100), 118 (3), 102 (7), 91 (7), 77 (14).

HRMS [ESI(+)]: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_9F_3O_2Na$: 253.0447; found: 253.0549.

4-Ethoxy-4*H*-thiochromene (8b)

Following typical procedure 2 using 2*H*-thiochromene (**5b**; 0.120 g, 0.810 mmol), TEOF (6 mL), and HTIB (0.350 g, 0.891 mmol). Purification by column chromatography (silica gel) gave **8b** (0.93 g, 0.48 mmol, 60%) as a light yellow oil.

IR (film): 3057, 3035, 2975, 2892, 2873, 1945, 1920, 1719, 1675, 1639, 1627, 1586, 1471, 1439 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.0 Hz, 3 H), 3.36 (dq, *J* = 9.1, 7.0 Hz, 1 H), 3.75 (dq, *J* = 9.1, 7.0 Hz, 1 H), 5.29 (d, *J* = 6.4 Hz, 1 H), 6.14 (dd, *J* = 10.2, 6.4 Hz, 1 H), 6.84 (d, *J* = 10.2 Hz, 1 H), 7.10–7.35 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8, 61.5, 75.0, 119.7, 125.2, 127.1, 128.2, 129.2, 129.7, 129.9, 130.1.

HRMS [ESI(+)]: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}OSNa$: 215.0501; found: 215.0498.

Anal. Calcd for $C_{11}H_{12}OS$: C, 68.71; H, 6.29. Found: C, 68.65; H, 6.31,

***cis*-3,4-Dimethoxy-4-methyl-3,4-dihydro-2*H*-chromene (11c)**

Following typical procedure 1 using methylchromene **5c** (0.202 g, 1.38 mmol), MeOH (6 mL), and HTIB (0.595 g, 1.51 mmol). Purification by column chromatography (silica gel) gave **11c** (0.183 g, 0.878 mmol, 64%) as a colorless oil.

IR (film): 3069, 3036, 2981, 2938, 2896, 2826, 1628, 1608, 1582, 1488 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.56 (s, 3 H), 3.08 (s, 3 H), 3.50 (s, 3 H), 3.60 (dd, *J* = 6.0, 2.8 Hz, 1 H), 4.12 (dd, *J* = 11.4, 6.0 Hz, 1 H), 4.32 (dd, *J* = 11.4, 2.6 Hz, 1 H), 6.82 (dd, *J* = 8.1, 1.3 Hz, 1 H), 6.86–6.94 (m, 1 H), 7.12–7.21 (m, 1 H), 7.31 (dd, *J* = 7.6, 1.7 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0, 49.8, 57.6, 62.8, 74.4, 76.1, 116.5, 120.1, 123.0, 127.8, 129.0, 154.1.

LRMS: *m*/*z* (%) = 208 ($M^{+\bullet}$, 3), 176 (13), 161 (13), 145 (49), 131 (79), 115 (52), 105 (49), 91 (34), 77 (48), 63 (44), 51 (53), 32 (100).

HRMS [ESI(+)]: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}O_3Na$: 231.0992; found: 231.0995.

***cis*-3,4-Diethoxy-4-methyl-3,4-dihydro-2*H*-chromene (12c)**

Following typical procedure 2 using methylchromene **5c** (0.160 g, 1.109 mmol), TEOF (6 mL), and HTIB (0.478 g, 1.22 mmol). Purification by column chromatography (silica gel) gave **12c** (0.152 g, 0.643 mmol, 58%) as colorless oil.

IR (film): 3069, 3036, 2976, 2932, 2880, 1608, 1583, 1486, 1446 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7 Hz, 3 H), 1.22 (t, *J* = 7 Hz, 3 H), 1.59 (s, 3 H), 3.19–3.32 (m, 2 H), 3.67–3.81 (m, 3 H), 4.06 (dd, *J* = 11.2, 7.0 Hz, 1 H), 4.32 (dd, *J* = 11.2, 3.2 Hz, 1 H), 6.81 (dd, *J* = 8.2, 1.2 Hz, 1 H), 6.86–6.96 (m, 1 H), 7.17 (ddd, *J* = 8.1, 7.2, 1.7 Hz, 1 H), 7.34 (dd, *J* = 7.8, 1.6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.5, 15.7, 22.4, 57.6, 64.4, 65.7, 74.2, 75.0, 116.5, 120.5, 124.5, 127.8, 129.0, 154.3.

LRMS: *m*/*z* (%) = 236 ($M^{+\bullet}$, 4), 164 (45), 147 (14), 136 (35), 121 (100), 105 (7), 91 (12), 77 (9), 65 (9), 43 (21).

HRMS [ESI(+)]: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}O_3Na$: 259.1305; found: 259.1306.

4-[Bis(2,2,2–trifluoroethoxy)methyl]-3,4-dihydro-2*H*-chromene (13d)

Following the typical procedure 3 using dihydro-1-benzoxepine **5d** (0.146 g, 1.00 mmol), TFE (6 mL), and HTIB (0.43 g, 1.1 mmol). Purification by column chromatography (silica gel, 2% EtOAc–hexanes) gave **13d** (0.172 g, 0.500 mmol, 50%) as a colorless oil.

IR (film): 3073, 3040, 2948, 2899, 1716, 1622, 1608, 1582, 1569, 1491, 1454 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.00–2.2 (m, 2 H), 3.06–3.11 (m, 1 H), 3.78–4.01 (m, 4 H), 4.10–4.26 (m, 2 H), 4.85 (d, *J* = 7.2 Hz, 1 H), 6.81–6.84 (m, 1 H), 6.89 (dd, *J* = 7.5, 1.2 Hz, 1 H), 7.13–7.18 (m, 1 H), 7.26 (dd, *J* = 7.8, 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 36.6, 62.6 (q, *J* = 139.5 Hz, OCH_2CF_3), 63.1, 64.8 (q, *J* = 138.6 Hz, OCH_2CF_3), 105.8, 117.2, 119.0, 120.3, 123.1 (q, *J* = 1105.8 Hz, OCH_2CF_3), 123.6 (q, *J* = 1104.6 Hz, OCH_2CF_3), 128.7, 130.8, 155.0.

LRMS: *m*/*z* (%) = 344 ($M^{+\bullet}$, 7), 245 (6), 211 (76), 145 (18), 133 (100), 115 (13), 105 (73), 83 (63), 77 (44), 51 (25), 39 (14).

HRMS [ESI(+)]: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{14}F_6O_3Na$: 367.0739; found: 367.0753.

(3,4-Dihydro-2*H*-chromen-4-yl)methanol (14d) and 4-[Bis(tosyloxy)methyl]-3,4-dihydro-2*H*-chromene (15d); Typical Procedure 4

A mixture of **5d** (0.155 g, 1.06 mmol) at 0 °C was stirred with HTIB (0.431 g, 1.10 mmol) for 5 min in HFIP–CH_2Cl_2 (1:4, 5 mL) and H_2O (0.4 mL, 22 equiv) (TLC monitoring). When the starting material had been consumed, $NaBH_4$ (5 equiv) was added. This mixture was stirred for 2 h at r.t. When the reaction was complete, H_2O was added, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine and dried (anhyd $MgSO_4$), and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (2–15%, EtOAc–hexane) giving alcohol **14d** (0.152 g, 0.930 mmol, 87%) and **15d** (0.46 g, 0.10 mmol, 9%).

(3,4-Dihydro-2*H*-chromen-4-yl)methanol (14d)

IR (film): 3437, 3071, 3036, 2928, 2878, 1607, 1580, 1490, 1453 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.70 (s, 1 H), 2.04–2.11 (m, 2 H), 2.95–3.03 (m, 1 H), 3.80 (dd, *J* = 11.0, 8.0 Hz, 1 H), 3.89 (dd, *J* = 10.8, 5.1 Hz, 1 H), 4.17–4.21 (m, 2 H), 6.83 (dd, *J* = 8.1, 1.2 Hz, 1 H), 6.87 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.09–7.18 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 36.0, 63.3, 66.4, 117.1, 120.3, 122.0, 127.9, 129.1, 155.2.

LRMS: *m*/*z* (%) = 164 ($M^{+\bullet}$, 30), 133 (100), 131 (15), 105 (66), 103 (21), 77 (34), 63 (6), 51 (16), 39 (20).

HRMS [ESI(+)]: *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{12}O_2Na$: 187.0735; found: 187.0741.

4-[Bis(tosyloxy)methyl]-3,4-dihydro-2*H*-chromene (15d)

IR (film): 3066, 3040, 2975, 2929, 2591, 1935, 1914, 1597, 1584, 1492 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.97–2.09 (m, 1 H), 2.21–2.30 (m, 1 H), 2.40 (s, 3 H), 2.45 (s, 3 H), 3.25–3.29 (m, 1 H), 4.01–4.13 (m, 2 H), 6.59 (d, *J* = 4.5Hz, 1 H), 6.66–6.71 (m, 2 H), 6.95 (ddd, *J* = 8.1, 1.5, 0.9 Hz, 1 H), 7.05–7.11 (m, 1 H), 7.12–7.16 (m, 2 H), 7.28–7.33 (m, 2 H), 7.40 (t, *J* = 1.8 Hz, 1 H). 7.42 (t, *J* = 1.8 Hz, 1 H), 7.75 (t, *J* = 1.8 Hz, 1 H), 7.77 (t, *J* = 1.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 21.6, 21.7, 38.5, 63.5, 100.3, 109.7, 117.1, 117.3, 120.4, 127.7 (2 C), 128.1 (2 C), 128.6, 129.6 (2 C), 129.8 (2 C), 132.7, 133.0, 145.1, 145.4, 155.3.

HRMS [ESI(+)]: *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{24}O_7S_2Na$: 511.0856; found: 511.0858.

1-(3,4-Dihydro-2*H*-chromen-4-yl)ethanone (16e)

Following typical procedure 3 using methylbenzoxepine **5e** (0.135 g, 0.843 mmol), HTIB (0.363 g, 0.930 mmol), and TFE (6 mL). Purification by column chromatography (silica gel, 10% EtOAc–hexanes) gave **16e** in (0.86 g, 0.49 mmol, 58%) as a colorless oil.

IR (film): 3067, 3070, 2967, 2930, 2885, 1708, 1607, 1581, 1490, 1453 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.05–2.15 (m, 1 H), 2.20 (d, *J* = 0.3 Hz, 3 H), 2.22–2.32 (m, 1 H), 3.80 (t, *J* = 6 Hz, 1 H), 4.12–4.24 (m, 2 H), 6.84–6.87 (m, 1 H), 6.90 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.06 (dddd, *J* = 7.5, 1.5, 0.9, 0.3 Hz, 1 H), 7.14–7.20 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5, 28.0, 48.5, 63.8, 117.4, 119.0, 120.5, 128.7, 130.0, 154.7, 208.8.

LRMS: *m*/*z* (%) = 176 ($M^{+\bullet}$, 58), 148 (9), 133 (42), 120 (100), 105 (8), 91 (94), 77 (23), 65 (18), 51 (19), 39 (34).

HRMS [ESI(+)]: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{12}O_2Na$: 199.073; found: 199.0743.

(2,2-Dimethyl-2,3-dihydrobenzofuran-3-yl)methanol (17f)

Following typical procedure 4 using dimethylchromene **5f** (0.192 g, 1.20 mmol), HTIB (0.517g, 1.32 mmol), HFIP–CH_2Cl_2 (1:4, 5 mL), and H_2O (22 equiv) at 0 °C. $NaBH_4$ was added in excess (5 equiv). Purification by column chromatography (silica gel, 15% EtOAc–hexane), gave **17f** (0.66 g, 0.37 mmol, 31%) as a colorless oil.

IR (film): 3452, 2973, 2930, 2874, 1611, 1596, 1482, 1461 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 3 H), 1.48 (s, 3 H), 1.84 (s, 1 H), 3.21 (t, *J* = 6.6 Hz, 1 H), 3.87 (d, *J* = 6.8 Hz, 2 H), 6.75 (d, *J* = 7.8 Hz, 1 H), 6.84 (td, *J* = 7.4, 0.8 Hz, 1 H), 7.10–7.25 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 29.3, 53.0, 62.6, 88.4, 109.8, 120.0, 124.8, 128.1, 128.7, 158.5.

LRMS: *m*/*z* (%) = 178 ($M^{+\bullet}$, 33), 147 (100), 131 (17), 119 (47), 107 (13), 91 (49), 77 (18), 65 (7), 51 (8), 39 (14).

HRMS [ESI(+)]: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{14}O_2Na$: 201.0886; found: 201.0879.

3-(Dimethoxymethyl)-2,2-dimethyl-2,3-dihydrobenzofuran (18f)

Following typical procedure 1 using dimethylchromene **5f** (0.142 g, 0.890 mmol), HTIB (0.382 g, 0.980 mmol), and MeOH (6 mL). Purification by column chromatography (silica gel, 2–5% EtOAc–hexanes) gave **18f** (0.60 g, 0.27 mmol, 30%) as a colorless oil.

IR (film): 3045, 2974, 2934, 2831, 1610, 1594, 1478, 1460 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.55 (s, 3 H), 3.41 (s, 3 H), 3.43 (s, 3 H), 3.44 (d, *J* = 5.1 Hz, 1 H), 4.52 (d, *J* = 5.1 Hz, 1 H), 6.72 (dt, *J* = 4.8, 0.3 Hz, 1 H), 6.83 (td, *J* = 4.5, 0.6 Hz, 1 H), 7.11–7.15 (m, 1 H), 7.34 (dtd, *J* = 4.5, 0.9, 0.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 29.0, 52.2, 52.3, 53.8, 88.3, 103.9, 109.5, 120.1, 126.3, 128.5, 158.7.

LRMS: *m*/*z* (%) = 222 ($M^{+\bullet}$, 2), 159 (8), 131 (4), 91 (5), 75 (100), 45 (7).

HRMS [ESI(+)]: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{18}O_3Na$: 245.1148; found: 245.1140.

1-(2,2-Dimethyl-2,3-dihydrobenzofuran-3-yl)ethanone (19g)

Following typical procedure 1 using trimethylchromene **5g** (0.120 g, 0.690 mmol), HTIB (0.297 g, 0.760 mmol), and MeOH (6 mL). Purification by column chromatography (silica gel, 2–4% EtOAc–hexane) gave **19g** in (0.031 g, 0.16 mmol, 24%) as a colorless oil.

IR (film): 3050, 2979, 2934, 2873, 1704, 1610, 1596, 1480, 1460 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.43 (s, 3 H), 1.52 (s, 3 H), 2.05 (s, 3 H), 3.88 (s, 1 H), 6.83 (d, *J* = 8 Hz, 1 H), 6.91 (dd, *J* = 7.4, 1 Hz, 1 H), 7.14 (d, *J* = 7.4 Hz, 1 H), 7.18–7.27 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.3, 29.4, 65.4, 88.4, 11.4, 120.8, 125.9, 126.1, 129.5, 159.2, 207.4.

LRMS: *m*/*z* (%) = 190 ($M^{+\bullet}$, 15), 147 (100), 131 (20), 119 (55), 103 (7), 91 (50), 77 (18), 63 (6), 51 (10), 43 (61).

HRMS [ESI(+)]: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{14}O_2Na$: 213.0886; found: 213.0877.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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