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Enantioselective Synthesis of 3,4-Chromanediones *via* Asymmetric Rearrangement of 3-Allyloxyflavones

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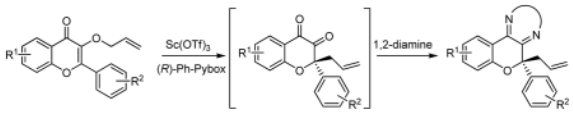
Abstract



Asymmetric scandium (III)-catalyzed rearrangement of 3-allyloxyflavones was utilized to prepare chiral, non-racemic 3,4-chromanediones in high yields and enantioselectivities. These synthetic intermediates have been further elaborated to novel heterocyclic frameworks including angular pyrazines and dihydropyrazines. The absolute configuration of rearrangement products was initially determined by a nonempirical analysis of circular dichroism (CD) using time-dependent density functional theory (TDDFT) calculations and verified by x-ray crystallography of a hydrazone derivative. Initial studies of the mechanism support an intramolecular rearrangement pathway that may proceed through a benzopyrylium intermediate.

Introduction

Enantioselective construction of quaternary stereogenic carbons is a significant challenge in organic chemistry.1 As part of our investigations concerning novel scaffolds, we encountered an interesting chemotype bearing two adjacent, fully substituted carbon centers present in cytotoxic, prenylated flavonoids including sanggenon A (**1**) and sanggenol F (**2**) (Figure 1).2 Further examination of their structures inspired the development of metal-catalyzed, asymmetric rearrangement 3› 4 of 3-allyloxyflavones **3** to 2-substituted 3,4-chromanediones **4**5 (Figure 2). Herein, we report the development of methodology to prepare chiral, non-racemic chromanediones using metal-catalyzed rearrangements6 of 3-allyloxyflavones and our initial studies to probe the reaction mechanism.

Results and Discussion

We began our investigation by evaluating reaction of 3-allyloxy flavone **5a** with a series of Lewis acids (Table 1). Among a panel of metals evaluated, trifluoromethanesulfonate salts of Lewis acidic metals were found to catalyze the reaction of **5a** to chromanedione **6a** in low to moderate yields employing 10 mol% of catalyst (entries 1, 2, and 7). However, complete

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Supporting Information Available: Complete experimental procedures and compound characterization data including is available free of charge via the Internet at http://pubs.acs.org.

conversion of allyloxy flavone **5a** was observed when 30 mol% of $Sc(OTf)_3$ was employed (entry 8). For purification purposes, the reactive 1,2-dicarbonyls **6a** were condensed with 1,2-ethylenediamine to afford dihydropyrazines **7**.7

Encouraged by these preliminary results, we investigated use of chiral ligands for $Sc(OTf)_3$ in the rearrangement. We found that the complex prepared using (*R*)-Ph-Pybox 10 as ligand8 led to good conversions and enantioselectivities to afford dihydropyrazines **7a,b** when the internal position of the olefin was substituted with a hydrogen (Table 1, entry 9) or methyl group (entry 10). In preliminary studies, flavone ether substrates bearing disubstituted alkenes (e.g. *Z* or *E* crotyl ethers) were found to be sluggish in rearrangements in contrast to catalytic asymmetric Claisen rearrangements of 2-alkoxycarbonyl-substituted allyl vinyl ethers reported by Hiersemann and coworkers.3e,f Unfortunately, rearrangements did not proceed when different substituents including bromine, phenyl, or carboxylates occupied the 2-position of the olefin.7 Furthermore, complexes of ligands **8** and **9** with $Sc(OTf)_3$ were found to be ineffective for the rearrangement.

Substrate Scope

Asymmetric rearrangement of a number of 3-allyloxyflavone substrates with diverse aryl substituents is shown in Table 2. Neither the position nor the electronic nature of substituents affected yields and enantioselectivities of reactions. For example, an electron-rich substituted allyloxyflavone (*p*-MeO, entry 10) afforded the same selectivity and yields as an electron poor substrate (*p*-NO_2, entry 14). Regarding the position of the substituents on the C-2 aryl ring, we found that the rearrangement tolerated the presence of electron-donating groups at C-2′ (entries 9 and 15). Use of 1,2-diamines that differed structurally and electronically in the condensation with the intermediate 3,4-chromanediones facilitated access to various heterocyclic structures including dihydropyrazines and pyrazines.

Absolute Configuration Assignment and Rationale

The absolute configuration of dichloropyrazine **25** was established by a nonempirical analysis of circular dichroism (CD) using time-dependent density functional theory (TDDFT) calculations.9 Prior to calculation of CD spectra, a conformational search using the MMFF94 was conducted on an arbitrarily chosen *S* absolute configuration of **25**. The resulting 12 conformers within a 10 kcal/mol energy window were optimized at the DFT/B3LYP/6-31G(d) level of theory, leading to three stable conformers within 1.5 kcal/mol (Figure 3).7 CD theoretical calculations were carried out for these three conformers at the TDDFT/B3LYP/6-31G(d) level of theory and the final spectrum obtained as the weighted average based on Boltzmann populations (Figure 3). The theoretical and observed CD spectra showed good agreement including a negative band at around 390 nm and a positive band at around 330 nm, thus unambiguously establishing the absolute configuration of **25** as *S*. The absolute configuration of **7b** produced from asymmetric rearrangement was studied in a similar manner (Table 1, entry 10).7 X-ray crystal structure analysis of a pyrazine-hydrazone **42** derived from (*S*)-(−)-**27** (Scheme 1)7 independently confirmed the absolute configuration of rearrangement products as determined by CD calculations.

Mechanistic Studies

To rationalize the observed enantioselectivity, we modeled the transition state of the presumed octahedral intermediate obtained by bidentate coordination of the 3,4-chromanedione to the scandium (III)-*(R)*-Ph-Pybox (Figure 4).10 The transition model suggests that the rearrangement occurs on the *Re*face of the double bond due to steric hindrance of the phenyl groups of the Ph-Pybox ligand (Figure 4). Further experiments were conducted using the deuterium-labeled substrate 3-(1,1-dideuteuroallyl-oxy)-chromen-4-one

43. When 3-allyloxy flavone **43** was submitted to scandium (III)-catalyzed rearrangement, complete transfer of the deuterium to the terminal position of the olefin occurred. After condensation of the intermediate 3,4-chromanedione **44** with 1,2-dianiline **22a**, the deuterated dihydropyrazine **45** was produced (eqn 1, Figure 5). This result indicates that the rearrangement process proceeds *via* an intramolecular pathway.

In order to rule out the existence of an intermolecular reaction pathway, a crossover experiment was also conducted (Figure 5, eqn 2).7 A 1:1 mixture of non-labeled allyloxyflavone **5a** and deuterated 6-OMe derivative **46** subjected to the reaction conditions led to sole production of pyrazines **27** and **47.** The absence of any observed allyl crossover is consistent with an intramolecular rearrangement process.

We also performed experiments to investigate possible mechanistic pathways. Crossover and deuterium-labeling experiments are consistent with asymmetric [3,3]-sigmatropic rearrangement3 of the scandium (III)-complexed flavone ether **48** to afford 3,4-chromanedione **44** (Figure 6). In an alternative pathway, the corresponding benzopyrylium11 **49** derived from delocalization of the positive charge and aromatization may undergo a [2,3] sigmatropic rearrangement12 to **50** followed by a stereospecific [1,2]-allyl shift.13,14 In the latter case, the deuterium atoms would also be located on the terminal position of the double bond. In order to probe the latter mechanism, we prepared 4-siloxy-1-benzopyrylium salt **51** by treatment of 3-methoxyflavone with TBSOTf 15 and determined that it has a characteristic fluorescence emission (450 nm) upon excitation at 410 nm16 (Figure 7). Similar fluorescence emissions observed for the $Sc(OTf)_3$-3-methoxyflavone complex **52** (excitation 400 nm) as well as the corresponding complex derived from 3-allyloxyflavone **5a**7 support the involvement of benzopyrylium intermediates after Lewis acid activation and a plausible alternative to the [3,3] mechanism for rearrrangement of 3-allyloxyflavones. Comparison of ^{13}C NMR spectra of **51** and complex **52** (Figure 8) also shows comparable downfield shifts for C-2 (3-methoxyflavone: 156 ppm; **51**: 162 ppm; **52**: 165 ppm), further supporting likely involvement of benzopyrylium intermediates in the asymmetric rearrangement of 3-allyloxyflavones.7

Conclusion

In summary, the asymmetric, scandium-catalyzed rearrangement of 3-allyloxyflavones has been utilized to prepare chiral, non-racemic 3,4-chromanediones in high yield and enantioselectivity. These reactive intermediates have been further elaborated to novel frameworks including angular pyrazines and dihydropyrazines. Initial mechanism studies support an intramolecular rearrangement pathway that may proceed through a benzopyrylium intermediate. Further applications of the methodology in both diversity- and target-oriented synthesis are currently under investigation and will be reported in due course.

Experimental Section

3-(Allyloxy)-2-phenyl-4*H*-chromen-4-one (5a)

To a suspension of commercially available 3-hydroxyflavone (1.00 g, 4.20 mmol, 1.0 equiv) in dry acetone (100 mL) was added at room temperature allyl bromide (0.54 mL, 6.30 mmol, 1.5 equiv, filtered through a plug of basic alumina), followed by K_2CO_3 (870.0 mg, 6.30 mmol, 1.5 equiv). The temperature was slowly increased to 65 °C and the reaction mixture was stirred overnight. The mixture was then cooled to room temperature and 30 mL of Et_2O was added. After filtration of the salts through a pad of Celite®, the solvent was removed *in vacuo* and the crude product was purified by column chromatography on silica gel. The allyloxyflavone **5a** was obtained as a white solid (1.14 g, 4.10 mmol, 97 %), after flash chromatography on silica gel (petroleum ether: ethyl acetate = 90: 10). M.p. (petroleum

ether: Et_2O) = 53–54 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.14-8.09 (m, 2H), 7.68 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.56-7.49 (m, 4H), 7.41 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 5.94 (tdd, *J* = 16.4, 10.3, 6.1 Hz, 1H), 5.28 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.15 (dd, *J* = 10.3, 1.2 Hz, 1H), 4.65 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ175.1, 156.0, 155.2, 139.9, 133.5, 133.4, 131.0, 130.6, 128.7 (2C), 128.4 (2C), 125.8, 124.6, 124.1, 118.5, 118.0, 73.2. IR ν_{max} (film): 3062, 2937, 1640, 1614, 1467, 1393, 1236, 1200, 1145, 993, 691 cm^{-1}. HRMS (ESI+) m/z calculated for $C_{18}H_{15}O_3$ 279.1021 found 279.1016 (M+H).

General Procedure for Sc(OTf)$_3$-*(R)*-Pybox-Ph-mediated Rearrangement

To a suspension of molecular sieves (4Å, 250.0 mg, flame-dried under high vacuum) was added, *via* cannula, a pre-stirred solution of $Sc(OTf)_3$ (23 mg, 0.05 mmol, 0.30 equiv) and (*R*,*R*)-(+)-2,6-bis(4-phenyl-2-oxazolinyl)pyridine **10** (20 mg, 0.05 mmol, 0.33 equiv) in DCE (3 mL). After stirring the suspension at rt for 2 h, a solution of allyloxyflavone **5a** (0.16 mmol, 1.0 equiv) in DCE (2 mL) was slowly added *via* cannula. The mixture was stirred at room temperature for 30 min and stirred overnight at 35 °C. 1,2-Ethylene diamine **24** (27 μL, 0.40 mmol, 2.50 equiv) was added in one portion and the mixture was allowed to stir for an additional 2 h at room temperature. After removal of the molecular sieves by filtration of the crude mixture through a pad of Celite, the solvent was evaporated *in vacuo* and the pyrazines **25** or dihydropyrazines **7** and **28** were isolated by flash column chromatography on silica gel.

(S)-5-Allyl-5-phenyl-3,5-dihydro-2*H*-chromeno[4,3-*b*] pyrazine (7a)

Purification on silica gel (petroleum ether: ethyl acetate = 80: 20) afforded dihydropyrazine **7a** as a bright yellow oil (47 mg, 0.16 mmol, 98 %). $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) = + 52.3°. er = 93:7 (ChiralCel OD 1% IPA in hexane, retention time 4.58: 5.47 min, major: minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.38 (ddd, *J* = 8.3, 7.2, 1.7 Hz, 1H), 7.30-7.15 (m, 5H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.95 (app t, *J* = 7.6 Hz, 1H), 5.94-5.81 (m, 1H), 5.06 (app d, *J* = 15.9 Hz, 1H), 5.05 (app d, *J* = 10.6 Hz, 1H), 4.14-3.95 (m, 2H), 3.49-3.25 (m, 2H), 3.13 (dd, *J* = 14.7, 6.6 Hz, 1H), 2.92 (dd, *J* = 14.7, 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 156.0, 149.6, 139.3, 133.1, 132.6, 128.4 (2C), 127.7, 126.0 (2C), 124.9, 122.0, 119.9, 118.4, 118.3, 85.6, 45.9, 44.4, 43.7. IR ν_{max} (film): 3074, 2943, 2841, 1608, 1593, 1461, 1384, 1330, 1220, 1118, 993, 914, 703 cm^{-1}. HRMS (ESI+) m/z calculated for $C_{20}H_{19}N_2O$ 303.1497 found 303.1492 (M+H).

(*S*)-5-(2-Methylallyl)-5-phenyl-3,5-dihydro-2*H*-chromeno[4,3-*b*]pyrazine (7b)

Dihydropyrazine **7b** was obtained from the rearrangement of the methallyloxyflavone **5b** (47 mg, 0.16 mmol, 1.0 equiv) after condensation of the intermediate 3,4-chromanedione **6b** with 1,2-ethylene diamine **24** (27 μL, 0.40 mmol, 2.5 equiv). Purification on silica gel (petroleum ether: ethyl acetate = 80: 20) afforded the title compound **7b** as a bright yellow oil (290 mg, .09 mmol, 57 %).$[\alpha]_D^{25}$ (*c* 0.5, $CHCl_3$) = + 16.8°. er = 98:2 (ChiralPak AD 1% IPA in hexane, retention time 6.05: 7.26 min, major: minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br d, *J* = 7.5 Hz, 1H), 7.39 (app t, *J* = 7.8 Hz, 1H), 7.30-7.16 (m, 5H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.96 (app t, *J* = 7.6 Hz, 1H), 4.79 (br s, 1H), 4.57 (br s, 1H), 4.07 (ddd, *J* = 16.1, 5.2, 4.0 Hz, 1H), 3.96 (ddd, *J* = 15.3, 4.4, 1.8 Hz, 1H), 3.42 (ddd, *J* = 16.9, 15.2, 4.9 Hz, 1H), 3.30 (ddd, *J* = 16.8, 15.5, 4.9 Hz, 1H), 3.08 (d, *J* = 14.4 Hz, 1H), 2.95 (d, *J* = 14.4 Hz, 1H), 1.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 155.9, 149.5, 140.5, 139.1, 133.0, 128.2 (2C), 127.5, 126.2 (2C), 124.9, 121.9, 120.0, 118.2, 115.7, 86.1, 46.2, 45.8, 44.6, 24.7. IR ν_{max} (film): 3070, 2944, 2845, 1609, 1593, 1461, 1328, 1219, 1118, 994, 895, 699 cm^{-1}. HRMS (ESI+) m/z calculated for $C_{21}H_{21}N_2O$ 317.1654 found 317.1679 (M+H).

(S)-6-Allyl-9,10-dichloro-6-phenyl-6*H*-chromeno[3,4-*b*]quinoxaline (25)

Pyrazine **25** was obtained using 4,5-dichloro-*o*-phenylenediamine **22a** (71 mg, 0.40 mmol, 2.5 equiv) for the condensation step. Purification on silica gel (petroleum ether: dichloromethane = 80: 20) afforded the pyrazine **25** as a light yellow powder (52 mg, 0.12 mmol, 78 %). M.p. (petroleum ether: CH_2Cl_2) = 159–160 °C. $[\alpha]_D^{25}$ (*c* 1.2, $CHCl_3$) = − 245.0°. er = 93:7 (ChiralCel OD 0% IPA in hexane, retention time 9.78: 12.26 min, major: minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.24 (dd, *J* = 7.8, 1.7 Hz, 1H), 8.22 (s, 1H), 7.45 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 7.37-7.31 (m, 2H), 7.25-7.12 (m, 4H), 7.09 (ddd, *J* = 7.8, 7.3, 1.1 Hz, 1H), 5.91 (app tdd, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.18 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.06 (dd, *J* = 10.2, 2.0 Hz, 1H), 3.55 (dd, *J* = 14.6, 6.9 Hz, 1H), 3.23 (dd, *J* = 14.6, 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 152.3, 144.5, 141.3, 141.0, 140.2, 134.6, 133.5 (2C), 132.8, 130.0, 129.7, 128.2 (2C), 127.6, 125.9 (2C), 125.7, 122.6, 120.7, 119.0, 118.3, 85.5, 45.5. IR ν_{max} (film): 3076, 2918, 1609, 1586, 1560, 1486, 1467, 1453, 1339, 1223, 1182, 1152, 1108, 1028, 908, 884, 731, 700 cm^{-1}. HRMS (ESI+) m/z calculated for $C_{24}H_{17}Cl_2N_2O$ 419.0718 found 419.0676 (M+H).

(6S,7aS,11aS)-6-Allyl-6-phenyl-7a,8,9,10,11,11a-hexahydro-6*H*-chromeno[3,4-*b*]-quinoxaline (28)

Dihydropyrazine **28** was obtained using *(1S, 2S)*-cyclohexane-1,2-diamine **23** (46 mg, 0.40 mmol, 2.5 equiv) for the condensation step. Purification on silica gel (petroleum ether: ethyl acetate = 90: 10) afforded the title compound **28** as a bright yellow oil (49 mg, 0.14 mmol, 86 %). ^{1}H NMR analysis of the crude showed only one diastereomer. $[\alpha]_D^{25}$ (*c* 1.2, $CHCl_3$) = − 103.1°. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.37 (app t, *J* = 7.8 Hz, 1H), 7.23 (s, 2H), 7.22 (d, *J* = 3.4 Hz, 2H), 7.21-7.15 (m, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.93 (app t, *J* = 7.6 Hz, 1H), 5.88 (dddd, *J* = 17.0, 10.5, 7.4, 6.6 Hz, 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 5.03 (d, *J* = 10.4 Hz, 1H), 3.14 (dd, *J* = 14.6, 6.5 Hz, 1H), 2.95 (dd, *J* = 14.6, 7.4 Hz, 1H), 2.86 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.76 (ddd, *J* = 15.2, 11.0, 4.1 Hz, 1H), 2.53 (br d, *J* = 13.2 Hz, 1H), 2.41 (br d, *J* = 11.3 Hz, 1H), 1.98-1.84 (m, 2H), 1.69-1.57 (m, 1H), 1.55-1.39 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 156.1, 149.2, 139.2, 132.9 (2C), 128.3 (2C), 127.6, 126.0 (2C), 125.0, 121.8, 119.9, 118.3, 118.1, 85.5, 60.4, 59.1, 43.6, 33.9, 33.7, 25.6 (2C). IR ν_{max} (film): 3073, 2933, 2857, 1606, 1589, 1574, 1462, 1448, 1321, 1257, 1221, 1055, 993, 916, 710 cm^{-1}. HRMS (ESI+) m/z calculated for $C_{24}H_{25}N_2O$ 357.1967 found 357.1971 (M+H).

(*S*)-2-(6-phenyl-6*H*-chromeno[4,3-*b*]quinoxalin-6-yl)acetaldehyde (40)

Following a procedure published in the literature,17 aldehyde **40** was synthesized starting from pyrazine **27** (52 mg, 0.15 mmol, 1.0 equiv) and was obtained as a colorless oil (51 mg, 0.14 mmol, 97 %) after purification on silica gel (petroleum ether: Et_2O = 70: 30). $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) = − 180.0°. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (dd, *J* = 2.9, 1.9 Hz, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 8.17-8.12 (m, 2H), 7.83-7.73 (m, 2H), 7.43 (app t, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 2H), 7.24-7.16 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.12 (app t, *J* = 7.4 Hz, 1H), 3.88 (dd, *J* = 16.7, 1.9 Hz, 1H), 3.47 (dd, *J* = 16.6, 2.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 155.2, 149.9, 143.4, 142.5, 141.2, 140.6, 133.0, 130.5, 129.6, 129.4, 129.3, 128.5 (2C), 128.1, 125.9 (2C), 125.7, 123.0, 121.5, 118.3, 83.5, 53.6. IR ν_{max} (film): 3061, 2842, 2744, 1725, 1607, 1491, 1460, 1346, 1225, 1070, 704 cm^{-1}. HRMS (ESI+) m/z calculated for $C_{23}H_{17}N_2O_2$ 353.1290 found 353.1261 (M+H).

(*S*)-4-Benzyl-3-((*E*)-2-((*S*)-6-phenyl-6*H*-chromeno[4,3-*b*]quinoxalin-6-yl)ethylideneamino)oxazolidin-2-one (42)

Pyrazine-hydrazone **42** was prepared according to a procedure published in the literature18 starting from pyrazine-aldehyde **40** (51 mg, 0.14 mmol, 1.0 equiv) and hydrazine **41** (55 mg,

0.29 mmol, 2.0 equiv). After silica gel chromatography (petroleum ether: ethyl acetate = 60: 40), the title compound was obtained as colorless crystals (75 mg, 0.14 mmol, 99 %). M.p. (petroleum ether: Et_2O) = 162–164°C. $[\alpha]_D^{25}$ (*c* 1.2, $CHCl_3$) = − 83.1°. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.9 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 8.06 (app t, *J* = 5.4 Hz, 1H), 7.81-7.71 (m, 2H), 7.42 (app t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.25-7.13 (m, 5H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.10 (app t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 2H), 4.22 (dd, *J* = 8.2, 3.9 Hz, 1H), 4.18 (dd, *J* = 16.2, 7.9 Hz, 1H), 4.04 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.93 (dd, *J* = 15.1, 5.0 Hz, 1H), 3.74 (dd, *J* = 14.8, 6.5 Hz, 1H), 2.91 (dd, *J* = 13.9, 2.8 Hz, 1H), 2.60 (dd, *J* = 13.9, 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 153.9, 150.8, 150.3, 143.3, 142.4, 141.4, 140.9, 134.9, 133.0, 130.4, 129.4 (2C), 129.2, 129.1 (2C), 128.7 (2C), 128.4 (2C), 127.9, 127.1, 126.0 (2C), 125.6, 122.8, 121.3, 118.3, 84.7, 65.5, 56.8, 44.8, 36.1. IR ν_{max} (film): 3058, 3015, 2921, 1771, 1604, 1555, 1491, 1459, 1401, 1347, 1211, 1087, 1029, 704 cm^{-1}. HRMS (ESI+) m/z calculated for $C_{33}H_{27}N_4O_3$ 527.2083 found 527.2102 (M+H).

General Procedure for the Preparation of Deuterated Allyloxyflavones 43 and 46

To a solution of commercially available 3-hydroxyflavone (1.00 g, 4.20 mmol, 1.0 equiv) and (1,1-d_2-allyl)-alcohol19 (378 mg, 6.30 mmol, 1.50 equiv.) in dry THF (15 mL) was added triphenylphosphine (1.32 g, 5.04 mmol, 1.20 equiv). After complete dissolution of the phosphine, the temperature was brought to 0 °C and diisopropyl azodicarboxylate (DIAD, 1.0 mL, 5.04 mmol, 1.20 equiv) was added dropwise to the mixture *via* syringe. The reaction was stirred overnight at room temperature and quenched with sat. $NaHCO_3$ solution. After separation of the layers and extraction of the aqueous phase with ether, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified by column chromatography on silica gel (petroleum ether: ether = 50: 50) to afford deuterated allyloxy flavone **43** as a white solid (565 mg, 2.01 mmol, 48 %). Following the same procedure, the methoxy derivative **46** was prepared starting from commercially available 6-methoxyflavonol (536 mg, 2.00 mmol, 1.0 equiv) and was isolated as a white powder (186 mg, 0.60 mmol, 30 %) after purification on silica gel (petroleum ether: ether = 50: 50).

3-Methoxy-2-phenyl-4H-chromen-4-one (53)

To a solution of 3-hydroxyflavone (150 mg, 0.06 mmol) in dry acetone (6 mL) was added dimethyl sulfate (0.10 mL, 0.09 mmol) and K_2CO_3 (131 mg, 0.09 mmol), and the reaction mixture was refluxed overnight. The mixture was cooled to room temperature and filtered through a pad of Celite®. The solvent was removed *in vacuo* and the crude product purified by column chromatography on silica gel. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.21 (d, *J* = 8.1 Hz, 1H), 8.13-8.07 (m, 2H), 7.70 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.59-7.50 (m, 4H), 7.41 (dd, *J* = 7.8 Hz, 1H), 3.89 (s, 3H). ^{13}C (400 MHz, CD_2Cl_2) δ 175.3, 156.0, 155.8, 142.0, 134.0, 131.6, 131.2, 129.0, 129.0, 126.0, 125.2, 124.8, 118.6, 60.4. IR_{max} (film): 1640, 1614, 1467, 1383, 1213, 1147, 897, 759 cm^{-1}. HRMS (ESI+) m/z calculated for $C_{16}H_{13}O_3$ 253.0865 found 253.0857 (M+H).

4-(Tert-butyldimethylsilyloxy)-3-methoxy-2-phenylchromenylium triflate salt (51):20

To a solution of 3-methoxy-2-phenyl-4H-chromen-4-one **53** (10.0 mg, 0.04 mmol) in CD_2Cl_2 (1.0 mL) was added TBSOTf (9.6 μL, 0.04 mmol). The reaction mixture was stirred at 40 °C for 0.5 h. The crude mixture was directly used for NMR and UV/fluorescence studies without further purification. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.38 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.25 (d, *J* = 7.1 Hz, 2H), 7.95 (dd, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.69-7.59 (m, 4H), 3.86 (s, 3H), 1.00 (s); 0.88 (s) (9H total), 0.46, 0.03 (s, 6H). ^{13}C (500 MHz, CD_2Cl_2) δ 174.8, 162.0, 156.3, 140.9, 136.7, 133.5, 130.0, 129.8, 127.4, 126.1, 121.5,

119.1, 61.7, 26.0, 25.0, 18.6, −2.7, −4.0. IR_{max} (film): 3452 (br), 1736, 1245, 1186, 1029, 640 cm^{-1}.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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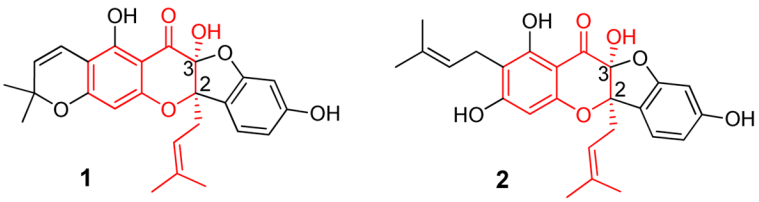


Figure 1.
Structures of sanggenon A and sanggenol F

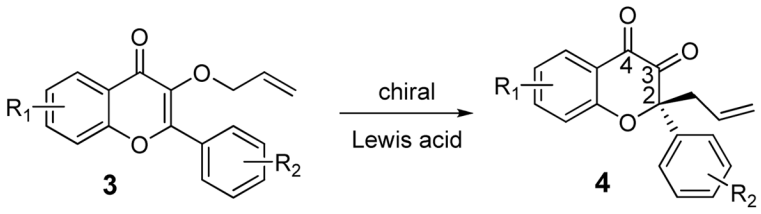


Figure 2.
Asymmetric rearrangement of 3-allyloxyflavones

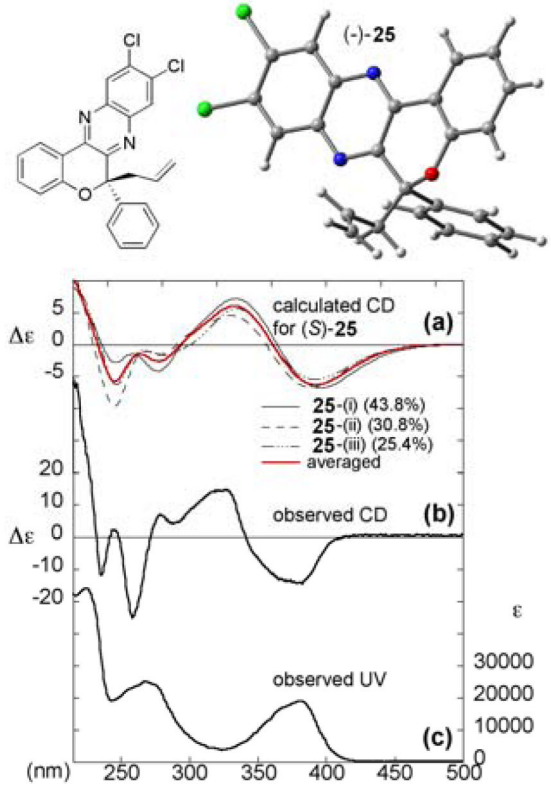


Figure 3.

Analysis of the absolute configuration of (−)-**25**. *Top*: the most stable conformer of (*S*)-**25**. *Bottom*: comparison of the calculated and the observed CD spectra of **25**. (a) Calculated CD spectra at the TDDFT/B3LYP/6-31G(d) for (*S*)-**25**. The Boltzmann populations of each conformer are shown in parentheses. (b) The observed CD and (c) UV spectrum obtained as an acetonitrile solution (0.04 mM). The observed CD spectrum is normalized to 100%ee. UVλ_{max} (ε): 225 (54000), 268 (25000), 382 (18900); CDλ_{ext} (Δε): 236 (−12.0), 258 (−25.1), 278 (+6.7), 327 (+14.8), 382 (−14.5). $[\alpha]_D^{25}$ = − 284.9 (c=1.2, $CHCI_3$).7

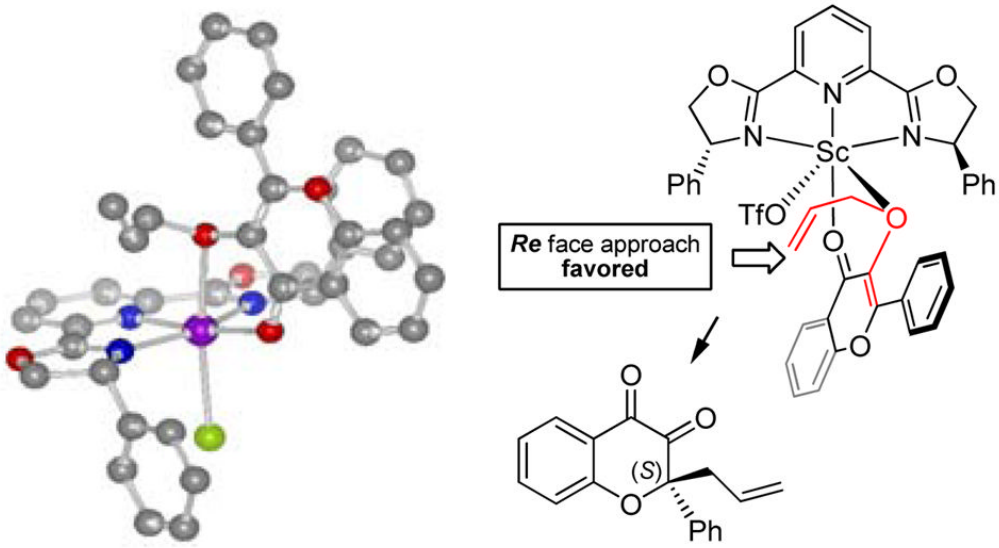


Figure 4.
Proposed transition state model

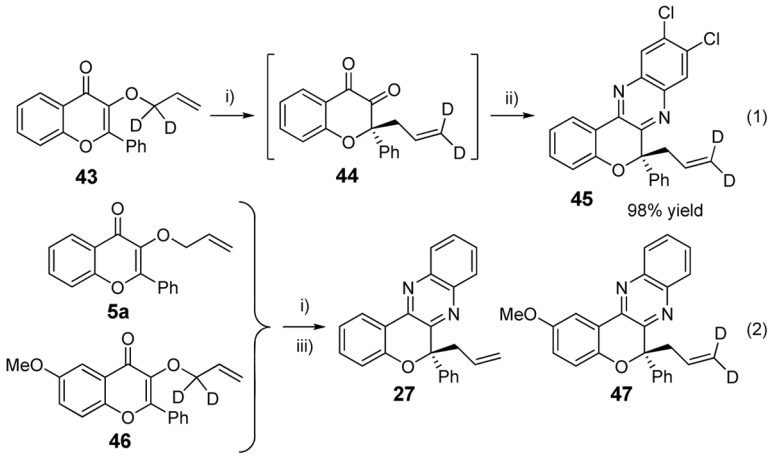


Figure 5.
Deuterium-labeled substrates and crossover experiment

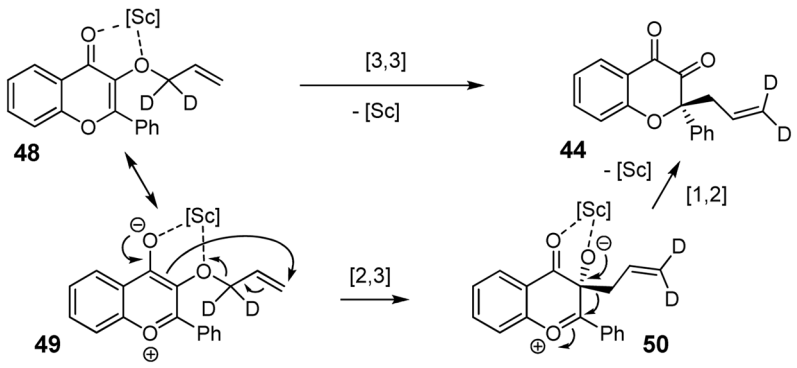


Figure 6.
Mechanistic Alternatives for the Asymmetric Rearrangement

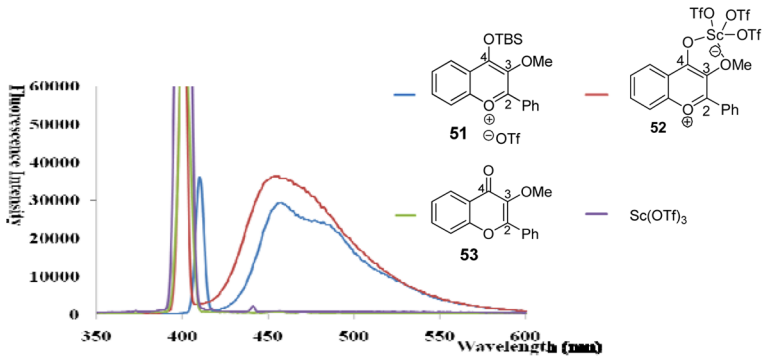


Figure 7.
Overlay of fluorescence spectra of **51**, **52**, **53**, and $Sc(OTf)_3$ (3.0×10^{-4} M in CH_2Cl_2).

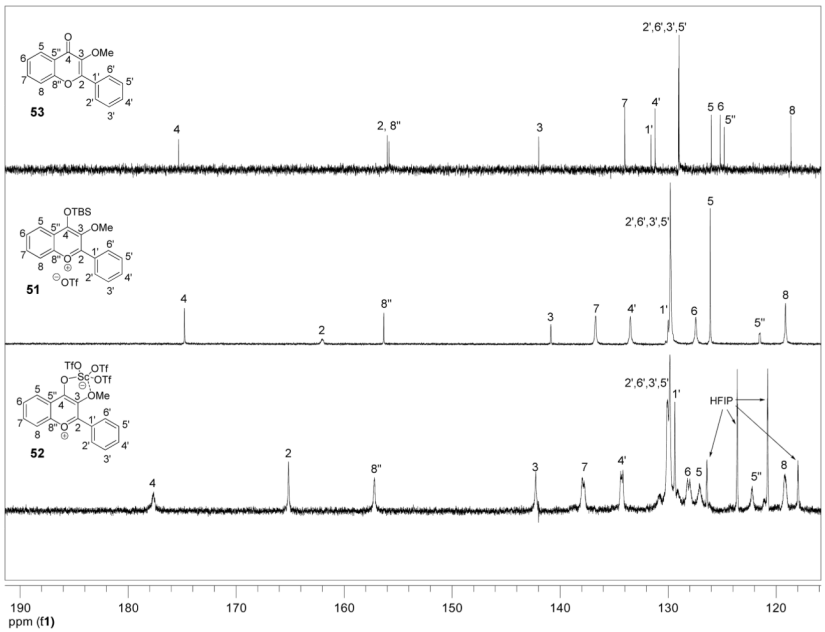
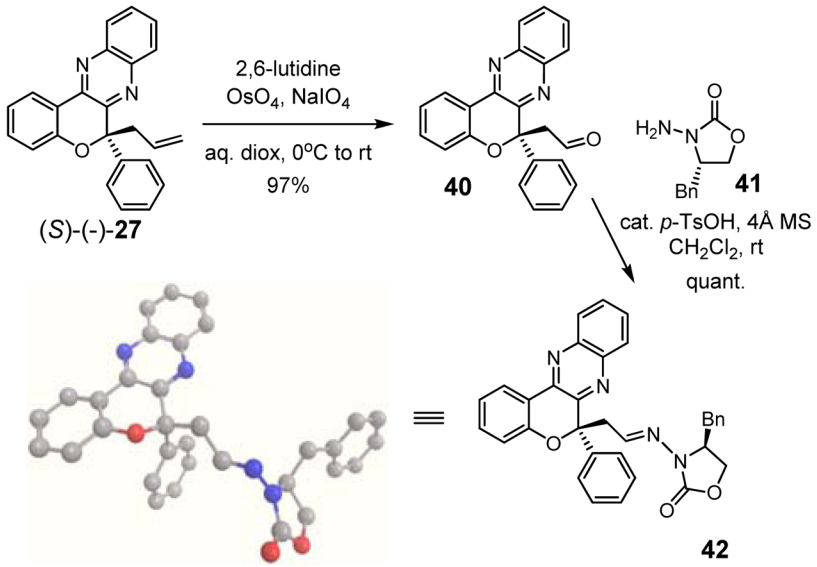


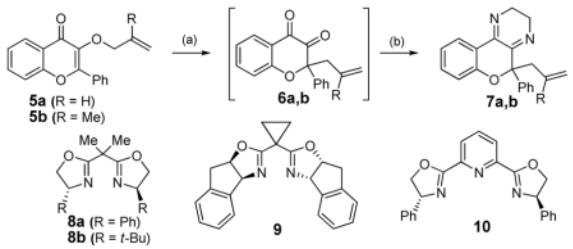
Figure 8.
Overlay of NMR spectra of **53**, **51**, and **52** in CD_2Cl_2, **52** with 4% by volume HPIF for solubility.



Scheme 1.
Synthesis and X-ray crystal structure analysis of pyrazine-hydrazone **42**

Table 1

Lewis Acid-Catalyzed Rearrangement[a]



entry	catalyst	Equiv (mol%)	ligand	Allyloxy flavone	% conversion (isolated yield 7)[b]	er[c]
1	$Lu(OTf)_3$	10	none	**5a**	16	-
2	$Cu(OTf)_2$	10	none	**5a**	50	-
3	$Cu(OTf)_2$	10	**8a**	**5a**	60	90:10
4	$Cu(OTf)_2$	10	**8b**	**5a**	_ [d]	-
5	$Cu(OTf)_2$	10	**9**	**5a**	_ [d]	-
6	$Cu(OTf)_2$	10	**10**	**5a**	_ [d]	-
7	$Sc(OTf)_3$	10	none	**5a**	38	-
8	$Sc(OTf)_3$	30	none	**5a**	98 (95)	-
9	$Sc(OTf)_3$	30	**10**	**5a**	100 (98)	97:3
10	$Sc(OTf)_3$	30	**10**	**5b**	82 (57)	98:2

[a] *Reaction conditions*: (a) 0.16 mmol 3-allyloxyflavone, 0.02–0.05 mmol catalyst, 0.02–0.05 mmol chiral ligand, and 250 mg of activated 4Å MS in DCE (0.04M) for 12 h under Ar at 35 °C; (b) 0.40 mmol of 1,2-ethylenediamine at rt for 2 h.

[b] Conversion determined by crude ^{1}H NMR analysis and isolated yields after column chromatography on silica gel.

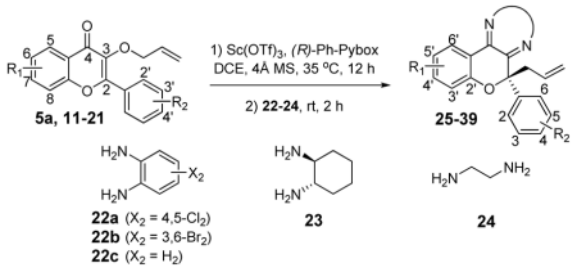
[c] Determined by chiral HPLC analysis.7

[d] No product isolated after column chromatography.

J Org Chem. Author manuscript; available in PMC 2011 July 1.

Table 2

Rearrangement Substrate Scope[a]



entry	substituents R^1, R^2	diamine	% yield [b]	product	er
1	H, H (**5a**)	**22a**	78	**25**	93:7
2	H, H (**5a**)	**22b**	98	**26**	- [d]
3	H, H (**5a**)	**22c**	93	**27**	93:7
4	H, H (**5a**)	**23**	86	**28**	>98:2 [c]
5	5-OMe, H (**11**)	**22c**	91	**29**	97:3
6	6-OMe, H (**12**)	**22c**	90	**30**	- [e]
7	7-OMe, H (**13**)	**24**	93	**31**	90:10
8	6-Me, H (**14**)	**24**	88	**32**	96:4
9	H, 2′-MeO (**15**)	**24**	96	**33**	95:5
10	H, 4′-MeO (**16**)	**24**	94	**34**	98:2
11	H, 4′-Me (**17**)	**24**	94	**35**	96:4
12	H, 4′-CF_3 (**18**)	**24**	86	**36**	95:5
13	H, 4′-Br (**19**)	**24**	93	**37**	91:9
14	H, 4′-NO_2 (**20**)	**24**	92	**38**	96:4
15	H, 2′-MeO-4′-Br (**21**)	**24**	80	**39**	96:4

[a] Reaction conditions: 0.16 mmol 3-allyloxyflavone, 0.05 mmol catalyst, 0.05 mmol (*R*)-Ph-Pybox, and 250 mg of activated 4Å MS in DCE (0.04 M) for 12 h under Ar at 35 °C, followed by reaction with 0.40 mmol of diamine at rt for 2 h.

[b] Isolated yields after column chromatography on SiO_2.

[c] Dr value provided.

[d] Separation of enantiomers *via* HPLC was not accomplished.

[e] Not determined.