

Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of 3-Fluorochromanone Derivatives to Access Enantioenriched *cis*-3-Fluorochroman-4-ols through Dynamic Kinetic Resolution

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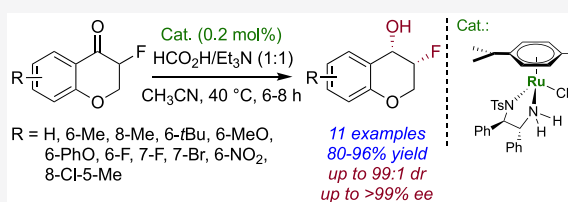
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ABSTRACT: Enantioenriched *cis*-3-fluoro-chroman-4-ol derivatives were conveniently prepared by the ruthenium-catalyzed asymmetric transfer hydrogenation of a new family of 3-fluoro-chromanones through a dynamic kinetic resolution process. The reaction proceeded under mild conditions using a low catalyst loading and HCO₂H/Et₃N (1:1) as the hydrogen source, affording the reduced fluorinated alcohols in good yields (80–96%), high diastereomeric ratios (up to 99:1 dr), and excellent enantioselectivities (up to >99% ee).



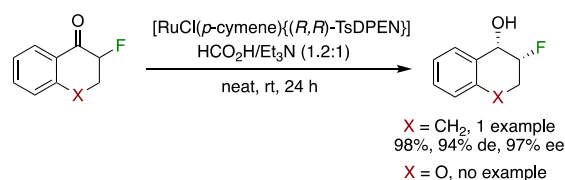
INTRODUCTION

Fluorine is an element that displays interesting qualities in drug design. Drug potency, permeability, pK_a, and clearance are some of the properties that can be modified by the introduction of a fluorine atom in a molecule.¹ For these reasons, the introduction of fluorine substituents into small molecules has been the subject of active research. On the other hand, chromanols are a group of oxygenated heterocycles belonging to the larger family of the naturally occurring homoisoflavonoids and are a privileged scaffold that appears in molecules of biological interest. This family of molecules possesses antibacterial, antiviral, and antitumoral activities.^{2,3} The addition of a fluorine atom into chromanols could thus foster and expand their biological effects and improve their versatility and utility as building blocks. Despite the great interest of fluorine, the difficulty of incorporating this element into building blocks has delayed the study and understanding of its effects along with its use; however, the field has experienced extensive progress over the past decades.⁴ Among the many challenges that organic chemists have faced in developing new ways of introducing fluorine into molecules, chirality is one of major importance. Organocatalysis, enzymatic kinetic resolution, and transition-metal catalysis have been deployed to access enantiomerically enriched compounds that contain fluorine-bearing stereocenters.^{5–8} Of these methods, the transition-metal-catalyzed asymmetric reduction of prochiral α -fluorinated ketones constitutes a straightforward pathway to chiral fluorohydrins. If the fluorine atom is positioned on a stereogenic carbon, the asymmetric reduction would then lead to enantiomerically enriched fluorohydrins with two contiguous stereogenic centers, provided an efficient dynamic kinetic resolution (DKR) can take place. Surprisingly, in this field only one example of α -fluorinated six-membered ring ketones has been reported by

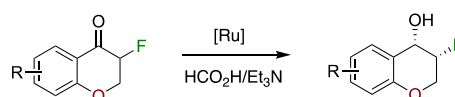
Lassaletta and co-workers for the asymmetric reduction of 2-fluoro-tetralone using Ru-catalyzed asymmetric transfer hydrogenation (Scheme 1).⁹ However, as far as 3-fluorochromanone derivatives are concerned, to our knowledge the asymmetric reduction of such compounds remains unexplored.

In the context of our ongoing studies directed toward the development of efficient methods for the asymmetric reduction of functionalized ketones¹⁰ and to access a wide range of enantioenriched 3-fluorochroman-4-ol derivatives, we report here the first ruthenium-catalyzed asymmetric transfer hydrogenation (ATH) of 3-fluorochromanones. Through a dynamic **Scheme 1. Catalytic Asymmetric Reduction of 2-Fluorotetralone and 3-Fluorochromanone Derivatives**

Previous work:^[9] ATH/DKR of 2-fluorotetralone



This work: ATH/DKR of 3-fluorochromanones



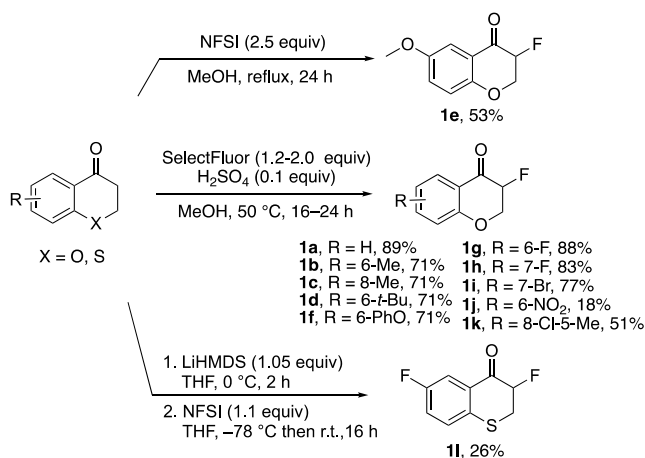
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kinetic resolution (DKR) process,^{11,12} the reaction sets two contiguous stereocenters in a single synthetic step and provides the targeted molecules in good yields with excellent levels of diastereo- and enantioselectivity.

RESULTS AND DISCUSSION

Our investigation of the asymmetric transfer hydrogenation of 3-fluorochromanone derivatives started with the preparation of novel racemic 3-fluorochroman-4-ones **1a–1k** bearing diverse electron-donating or electron-withdrawing groups on the aryl ring from the corresponding chromanones using either SelectFluor or NFSI as the fluoride source (Scheme 2).¹³ A difluorothiochromanone derivative **1l** was prepared as well. 3-

Scheme 2. Preparation of Substituted 3-Fluorochromanone Derivatives **1a–1k** and 3,6-Difluorothiochroman-4-one **1l**



Fluorochroman-4-one **1a** was next used as a standard substrate for the optimization of the reaction parameters (Table 1).

Based on our previous experience in ATH, the reduction was first carried out at 30 °C in dichloromethane in the presence of 1 mol % either Ru(II) or Rh(III) complexes (*R,R*)-**A**¹⁴ or (*R,R*)-**B**,¹⁵ respectively, with a formic acid/triethylamine (5:2) azeotropic mixture (FA/TEA, 3 equiv) as the hydrogen source (Table 1, entry 1 or 2). Under these conditions, full conversions were attained, and the reduced product *cis*-**2a** was obtained in a 95% yield in both cases. Although high enantioinduction was achieved, only low diastereoisomeric ratios of 58:42 and 55:45, respectively, were obtained. No effect was observed when the reaction was conducted at room temperature with complex (*R,R*)-**A** at a lower catalyst loading of 0.5 mol % (Table 1, entry 3 versus entry 1). We next performed the Ru-mediated ATH of 3-fluorochroman-4-one **1a** using 0.5 mol % (*R,R*)-**A** with a HCO₂H/Et₃N (1.2:1) mixture as the hydrogen donor (15 equiv), which also served as the solvent, at room temperature (Table 1, entry 4). However, 3-fluoro-4-chroman-4-one **1a** was unreactive using these reaction conditions. To overcome the lack of reactivity, a small amount of acetonitrile was added to the reaction mixture, affording a full conversion to provide *cis*-**2a** in a 95% isolated yield with a very high diastereomeric ratio of 97:3 and an enantiomeric excess of 99% (Table 1, entry 5). Under otherwise identical conditions, Rh(III) and Ru(II) complexes (*R,R*)-**B** and (*R,R*)-**C**,¹⁶ respectively, gave the reduced compound *cis*-**2a** with a lower diastereoselectivity and a lower yield (Table 1, entries 6 and 7).

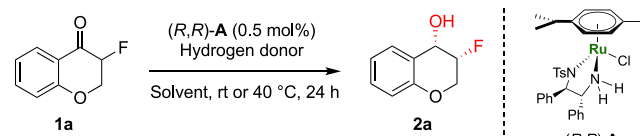
Table 1. Catalyst Screening for the ATH of **1a**^a

entry	catalyst	solvent	FA/TEA ratio	yield ^b (%)	dr ^c (<i>cis:trans</i>)	ee ^d (%)
1 ^e	(<i>R,R</i>)- A ^f	CH ₂ Cl ₂	5:2 ^g	95	58:42	95
2 ^e	(<i>R,R</i>)- B ^f	CH ₂ Cl ₂	5:2 ^g	95	55:45	92
3	(<i>R,R</i>)- A ^h	CH ₂ Cl ₂	5:2 ^g	95	58:42	95
4	(<i>R,R</i>)- A ⁱ	neat	1.2:1 ^j	—	—	—
5	(<i>R,R</i>)- A ⁱ	CH ₃ CN	1:1 ^j	95	97:3	99
6	(<i>R,R</i>)- B ⁱ	CH ₃ CN	1:1 ^j	92	81:19	97
7	(<i>R,R</i>)- C ⁱ	CH ₃ CN	1:1 ^j	87	96:4	>99

^aConditions are as follows: **1a** (0.60 mmol), catalyst (0.5 or 1.0 mol %), solvent (0.25 mL), HCO₂H/Et₃N (3–15 equiv), rt. ^bIsolated yield. ^cDetermined by ¹H NMR spectroscopy of the crude product after the ATH reaction. ^dee for the *cis*-product was determined by the SFC analysis. ^eThe reaction was carried out at 30 °C. ^fThe reaction was conducted with 1.0 mol % catalyst. ^gThe reaction was carried out with 3.0 equiv of HCO₂H/Et₃N (5:2). ^hThe reaction was conducted with 0.5 mol % catalyst. ⁱThe reaction was run with 15 equiv of HCO₂H/Et₃N (1.2:1). ^jThe reaction was run with 11 equiv of HCO₂H/Et₃N (1:1).

From the above results, the ruthenium complex (*R,R*)-**A** was selected as the catalyst for the remainder of the study. To further assess the scope of this ATH, we pursued the optimization of the reaction conditions by varying the solvent, the nature and amount of the hydrogen source, and the catalyst loading (Table 2).

Further experiments showed that the (*R,R*)-**A** catalyst efficiently reduced **1a** within 24 h. Still working with 0.5 mol % (*R,R*)-**A**, the ratio of the HCO₂H/Et₃N mixture was shown to have a crucial effect on the stereoselectivity of the reduction, as gradually decreasing the ratio from 5:2 to 1:1 resulted in a dramatic increase of the diastereomeric ratio from 67:33 to 97:3 in favor of the *cis*-product **2a** (Table 2, entries 1–3). The racemization of the substrate likely occurs by the keto–enol equilibrium and appears to be favored with a 1:1 ratio of base to acid. Other hydrogen donors such as HCO₂H/DBU (1:1) and HCO₂H/DABCO (1:1) were then evaluated (Table 2, entries 4 and 5, respectively). Whereas the former led to lower yield and dr as compared to those of HCO₂H/Et₃N (1:1), the latter afforded comparable results. The formic acid/triethylamine mixture was nevertheless selected as the hydrogen source for practical reasons, as it is commercially available. We next turned our attention to screening the solvents and confirmed that the ATH of **1a** was best achieved in acetonitrile since all the other explored solvents (CH₂Cl₂, toluene, AcOEt, *i*-PrOH, and THF) gave lower yields or diastereoselectivities, with enantioselectivities ranging from 91% to >99% ee (Table 2, entries 6–10, respectively). The influence of the amount of the HCO₂H/Et₃N (1:1) mixture was also investigated (Table 2, entries 11–13), and it turned out that while the use of 6

Table 2. Optimization of the Reaction Parameters^a


entry	solvent	hydrogen donor/ equivalents	yield ^b (%)	dr ^c	ee ^d (%)
1	CH ₃ CN	HCO ₂ H/Et ₃ N (5:2)/11	94	67:33	92
2	CH ₃ CN	HCO ₂ H/Et ₃ N (2:5)/11	92	81:19	98
3	CH ₃ CN	HCO ₂ H/Et ₃ N (1:1)/11	95	97:3	99
4	CH ₃ CN	HCO ₂ H/DBU (1:1)/11	84	92:8	98
5	CH ₃ CN	HCO ₂ H/DABCO (1:1)/11	96	96:4	99
6 ^e	CH ₂ Cl ₂	HCO ₂ H/Et ₃ N (1:1)/11	69	88:12	98
7 ^e	toluene	HCO ₂ H/Et ₃ N (1:1)/11	48	92:8	91
8	AcOEt	HCO ₂ H/Et ₃ N (1:1)/11	94	93:7	96
9 ^e	<i>i</i> -PrOH	HCO ₂ H/Et ₃ N (1:1)/11	56	93:7	>99
10	THF	HCO ₂ H/Et ₃ N (1:1)/11	96	92:8	95
11 ^f	CH ₃ CN	HCO ₂ H/Et ₃ N (1:1)/11	94	98:2	>99
12 ^f	CH ₃ CN	HCO ₂ H/Et ₃ N (1:1)/6	95	98:2	>99
13 ^{e,f}	CH ₃ CN	HCO ₂ H/Et ₃ N (1:1)/3	74	98:2	>99
14 ^{e,g}	CH ₃ CN	HCO ₂ H/Et ₃ N (1:1)/6	94	99:1	99
15 ^{e,h}	CH ₃ CN	HCO ₂ H/Et ₃ N (1:1)/6	73	99:1	>99

^aConditions are as follows: **1a** (0.60 mmol), (*R,R*)-**A** (0.5 mol %), hydrogen donor, solvent (0.25 mL), rt or 40 °C, 24 h. ^bIsolated yield of **2a**. ^cDetermined by ¹H NMR spectroscopy of the crude product after the ATH reaction. ^dee for the *cis*-product was determined by the SFC analysis. ^eIncomplete conversion. ^fUsed 1 mL of CH₃CN. ^gS/C = 500, 40 °C, 6 h. ^hS/C = 1000, 40 °C, 33 h.

equiv of HCO₂H/Et₃N (1:1) instead of 11 equiv had no effect, using 3 equiv was detrimental to the conversion rate, affording a lower yield of 74%. Finally, to complete the optimization of the reaction parameters, we progressively increased the S/C ratio from 200 to 1000 while running the reaction upon the gentle heating of the reaction mixture to 40 °C to ensure full conversion within a reasonable time (Table 2, entries 14 and 15, respectively). Although incomplete conversion was observed with a S/C ratio of 1000 even after a reaction time of 33 h (Table 2, entry 15), pleasingly the reaction proceeded in only 6 h with S/C = 500, affording compound *cis*-**2a** in a 94% yield, 99:1 dr, and 99% ee (Table 2, entry 14). On the basis of the above screening, the optimized conditions were set as follows: (*R,R*)-**A** (0.2 mol %) as the precatalyst and HCO₂H/Et₃N (1:1) (6 equiv) as the hydrogen donor in CH₃CN (0.6 M) at 40 °C.

Upon subjecting the racemic 3-fluorochroman-4-ones **1a**–**1k** to the optimized reaction conditions, the scope of the asymmetric transfer hydrogenation of a series of variously substituted 3-fluorochromanone derivatives was next evaluated (Table 3). Notably, compounds **1a**–**1k** bearing diverse electron-donating or electron-withdrawing groups on the aryl ring all yielded the expected *cis*-fluorohydrins **2a**–**2k** in 80–96% yields with uniformly high levels of diastereoselectivity (98:2 to 99:1 dr) and enantioselectivity (up to >99% ee) in 6–8 h of reaction time (Table 3). The ATH was tolerant of electron-donating substituents such as methyl, *tert*-butyl, methoxy, and phenoxy groups in various positions of the benzene ring (Table 3, entries 2–6, respectively). The substituted 3-fluorochromanone derivatives bearing electron-withdrawing substituents on the aryl ring such as fluoro,

bromo, and nitro groups underwent efficient reduction as well (Table 3, entries 7–10). The ATH of 3-fluorochromanone **1k** bearing a methyl group and a chlorine atom proceeded similarly with excellent diastereo- and enantioselectivities (Table 3, entry 11). To extend the substrate scope of the reaction, we performed the ATH on the 3-fluorothiochroman-4-one derivative **1l** as well. The corresponding *cis*-alcohol **2l** was obtained in an 80% yield with 92:8 dr and 99% ee (Table 3, entry 12).

The absolute configurations of compounds **2b** and **2k** were unambiguously assigned as (3*R*,4*S*) by the X-ray crystallographic analysis (Figure 1). By analogy, we conjectured that the remainder of the ATH products **2** followed the same trend.

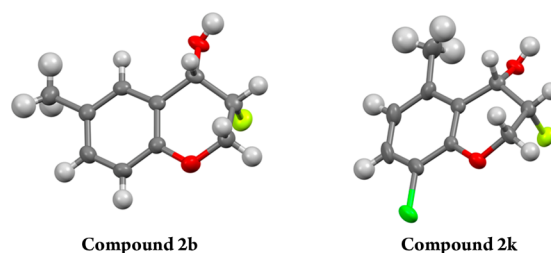


Figure 1. X-ray crystallographic structures of **2b** and **2k**. Displacement ellipsoids are shown at the 30% probability level.

The enantiocontrol in the ATH reaction of (±)-**1a** likely arises from the well-established edge-to-face arene–aryl interaction between the η⁶-arene and the aryl group of the chromanone through a transition state in which the ligand–substrate N–H–O=C bonding and the stabilizing CH–π interaction ensures a high enantiomeric excess (Figure 2).¹⁷

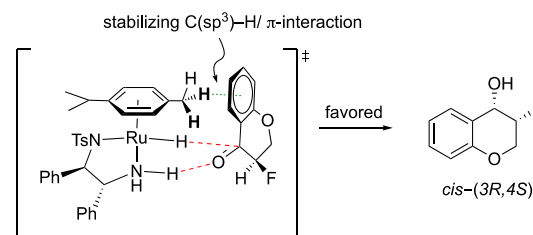


Figure 2. Proposed model for the absolute stereochemistry in the ATH of compound **1a**.

On the other hand, the preferential formation of the *cis*-isomer might be explained by a transition state wherein the catalyst would approach the ketone opposite the fluorine atom.

The efficiency of this ATH was supported by a scale-up experiment that was performed on a gram scale under the standard conditions with 3-fluorochroman-4-one **1a**. After a reaction time of 20 h, the desired (3*R*,4*S*)-3-fluorochroman-4-ol **2a** was isolated in a 98% yield with a diastereomeric ratio of 98:2 and >99% ee (Scheme 3).

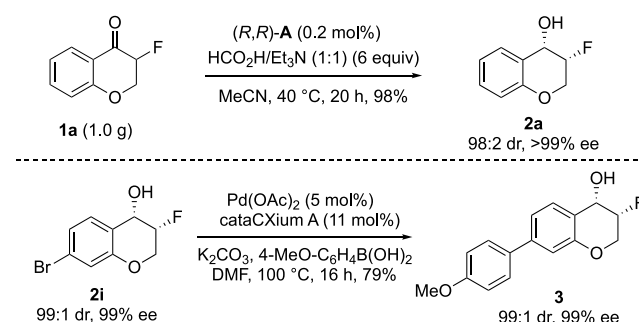
In addition, the postfunctionalization of (3*R*,4*S*)-7-bromo-3-fluorochroman-4-ol **2i** was also carried out using a Suzuki–Miyaura coupling with Pd(OAc)₂, cataCXium A as a ligand, K₂CO₃ as a base, and 4-methoxyphenylboronic acid to access the biaryl derivative **3** that was obtained in a 79% yield (Scheme 3).

Table 3. Substrate Scope of the ATH/DKR of the 3-Fluorochromanone and 3-Fluorothiochromanone Derivatives^a

entry/ATH product 2		Yield ^b (%)	dr ^c	ee ^d (%)
1/2a		94	99:1	>99
2/2b		92	98:2	98
3/2c		95	99:1	98
4/2d		80	98:2	98
5/2e		93	99:1	99
6/2f		96	98:2	92
7/2g		93	98:2	99
8/2h		95	98:2	98
9/2i		93	99:1	99
10/2j		92	98:2	98
11/2k		96	98:2	99
12/2l		80	92:8	99

^aConditions are as follows: 1a–1l (0.60 mmol), (*R,R*)-A (0.2 mol %), HCO₂H/Et₃N (1:1) (6 equiv), MeCN (1 mL), 40 °C, 6–8 h. ^bIsolated yield, complete conversion in all cases. ^cDetermined by ¹H NMR spectroscopy of the crude product after the ATH reaction. ^dee for the *cis*-product was determined by the SFC analysis.

Scheme 3. Scale-up Experiment and Post-Functionalization Reaction



CONCLUSION

In summary, we have developed an unexplored, operationally simple, and practical ruthenium-catalyzed asymmetric transfer hydrogenation of novel 3-fluorochromanone derivatives that allows for the installation of vicinal stereogenic centers in a single step. This approach, which has many advantages, appears to be a useful means to efficiently access enantiomerically enriched 3-fluorochroman-4-ols. This catalytic enantioselective route proceeds under mild conditions using a low catalyst loading (0.2 mol %) of the ruthenium complex (*R,R*)-A and HCO₂H/Et₃N (1:1) as the hydrogen source, delivering the reduced fluorinated compounds in good yields (80–96%), high diastereomeric ratios (up to 99:1 dr), and excellent enantioselectivities (up to >99% ee). Various electron-donating or electron-withdrawing groups with different substitution patterns on the aryl ring were well tolerated in this ATH reaction, affording a range of fluorinated building blocks. To extend the substrate scope of the reaction, we showed that the reaction was tolerant to the 3-fluorothiochroman-4-one derivative 1l as well. We demonstrated the ability of the asymmetric transfer hydrogenation to proceed under gram-scale conditions, verifying the usefulness of this transformation. Additionally, the enantiomerically enriched 3-fluorochroman-4-ols that are produced can serve as interesting scaffolds for further functionalization and as potential motifs of biological importance.

EXPERIMENTAL SECTION

General Information. All air or water sensitive reactions were carried out under an argon atmosphere. THF, DMF, CH₂Cl₂, and toluene were dried over alumina columns in a solvent purification apparatus (Innovative Technology). Methanol and acetonitrile from Sigma-Aldrich were used without further purification. The formic acid/triethylamine (1:1) mixture was purchased from either Fluka or Alfa Aesar and was used without further purification. Reactions were monitored by thin-layer chromatography carried out on precoated silica gel plates (Merck 60F254) and revealed with either an ultraviolet lamp ($\lambda = 254$ nm) or a potassium permanganate solution. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded using a Bruker AC 400 (400 MHz) spectrometer. The chemical shifts are expressed in parts per million (ppm) and referenced to residual chloroform (7.26 ppm). Data are reported as follows: chemical shifts (δ), multiplicity (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; quint, quintuplet; sext, sextuplet; hept, heptuplet; m, multiplet; and br, broad), coupling constants, and integration. Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded using a Bruker AC 400 (100 MHz) spectrometer. The chemical shifts are expressed in parts per million (ppm) relative to the center line of the triplet at 77.16 ppm for CDCl₃. Melting points (mp) were determined on a Kofler melting point apparatus. Optical

rotations were measured on a Jasco P-1010 polarimeter. High-resolution mass spectrometric (HRMS) analyses were measured on LTQ-Orbitrap (Thermo Fisher Scientific) spectrometer at Sorbonne Université.

Synthesis of Compounds 1a–1d and 1f–1k. 3-Fluorochroman-4-one 1a. To a 50 mL-round-bottom flask fitted with a stirrer and a condenser and set under argon were added chroman-4-one (1.0 g, 6.7 mmol, 1.0 equiv), SelectFluor (2.83 g, 8.0 mmol, 1.2 equiv), MeOH (4 mL), and conc. H_2SO_4 (36 μL , 0.7 mmol, 0.1 equiv). The resulting suspension was heated at 50 °C (oil bath) for 24–72 h (completion of the reaction was monitored by TLC; petroleum ether/ethyl acetate 80:20). After the reaction mixture was cooled, the slurry was diluted with 3 mL of methanol and filtered. The obtained solid was washed with MeOH (2×3 mL), and the filtrate was concentrated under reduced pressure. The resulting mixture was dissolved in CH_2Cl_2 (20 mL), washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate from 95:5 to 85:15) to yield **1a** as a white crystalline solid (1.02 g, 89%). mp 66–68 °C (lit. 66.5–67.3 °C). ^1H NMR (400 MHz, chloroform-*d*) δ 7.92 (dd, J = 7.9, 1.8 Hz, 1H), 7.54 (ddd, J = 8.7, 7.2, 1.8 Hz, 1H), 7.09 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 7.01 (dd, J = 8.4, 1.1 Hz, 1H), 5.17 (ddd, J = 47.0, 9.2, 4.7 Hz, 1H), 4.70–4.47 (m, 2H). $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, chloroform-*d*) δ –204.05. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, chloroform-*d*) δ 187.3 (C–F, $^2J_{\text{CF}}$ = 20.2 Hz), 187.1 (C–F, $^2J_{\text{CF}}$ = 20.2 Hz), 161.4, 136.9, 127.8, 122.5, 119.6, 118.0, 86.6 (C–F, $^1J_{\text{CF}}$ = 188.9 Hz), 84.7 (C–F, $^1J_{\text{CF}}$ = 188.9 Hz), 69.0 (C–F, $^2J_{\text{CF}}$ = 30.3 Hz), 68.7 (C–F, $^2J_{\text{CF}}$ = 30.3 Hz). IR (solid) ν 3073, 2360, 2341, 1700 (C=O), 1607, 1585, 1034, 1014 cm^{-1} . The data are in accordance with those previously reported in the literature.^{12a}

6-Methyl-3-fluorochroman-4-one 1b. Following the described procedure, 300 mg of 6-methylchroman-4-one (1.9 mmol, 1.0 equiv) was used. Purification via flash column chromatography on silica gel (90:10 petroleum ether/*tert*-butyl methyl ether) yielded 236 mg of **1b** as a white solid (71%). mp 60–62 °C. ^1H NMR (400 MHz, chloroform-*d*) δ 7.71 (d, J = 2.1 Hz, 1H), 7.35 (ddd, J = 8.5, 2.3, 0.6 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 5.15 (ddd, J = 47.0, 9.3, 4.7 Hz, 1H), 4.67–4.44 (m, 2H), 2.33 (s, 3H). $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, chloroform-*d*) δ –204.07. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, chloroform-*d*) δ 187.5 (C–F, $^2J_{\text{CF}}$ = 15.2 Hz), 187.4 (C–F, $^2J_{\text{CF}}$ = 15.2 Hz), 159.5, 138.1, 132.1, 127.3, 119.2, 117.8, 86.7 (C–F, $^1J_{\text{CF}}$ = 188.9 Hz), 84.9 (C–F, $^1J_{\text{CF}}$ = 188.9 Hz), 69.0 (C–F, $^2J_{\text{CF}}$ = 26.3 Hz), 68.7 (C–F, $^2J_{\text{CF}}$ = 26.3 Hz), 20.5. IR (solid) ν 2957, 2897, 1692, 1616 (C=O), 1488, 1416, 1080, 1029 cm^{-1} . The data are in accordance with those previously reported in the literature.^{12b}

8-Methyl-3-fluorochroman-4-one 1c. Following the described procedure, 180 mg of 8-methylchroman-4-one (1.1 mmol, 1.0 equiv) was used. Purification via flash column chromatography on silica gel (45:45:10 petroleum ether/toluene/MTBE and 90:10 petroleum ether/ethyl acetate) yielded 140 mg of **1c** as a yellow oil, which proceeded to solidify into a crystalline solid (71%). mp 40–42 °C. ^1H NMR (400 MHz, chloroform-*d*) δ 7.77 (dt, J = 8.1, 1.7 Hz, 1H), 7.39 (ddt, J = 7.3, 1.8, 0.9 Hz, 1H), 6.98 (td, J = 7.7, 1.9 Hz, 1H), 5.15 (ddd, J = 47.2, 9.3, 4.7 Hz, 1H), 4.74–4.49 (m, 2H), 2.25 (s, 3H). $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, chloroform-*d*) δ –204.18. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, chloroform-*d*) δ 187.7 (C–F, $^2J_{\text{CF}}$ = 15.2 Hz), 187.5 (C–F, $^2J_{\text{CF}}$ = 15.2 Hz), 159.6, 137.8, 127.5, 125.4, 122.0, 119.2, 86.6 (C–F, $^1J_{\text{CF}}$ = 187.9 Hz), 84.7 (C–F, $^1J_{\text{CF}}$ = 187.9 Hz), 68.8 (C–F, $^2J_{\text{CF}}$ = 26.3 Hz), 68.6 (C–F, $^2J_{\text{CF}}$ = 26.3 Hz), 15.7. IR (solid) ν 2989, 2881, 1695 (C=O), 1597, 1481, 1275, 1051, 1032 cm^{-1} . HRMS (APCI) m/z [M + H]⁺ calcd for $\text{C}_{10}\text{H}_9\text{FO}_2$ 181.0659, found 181.0659.

6-(*tert*-Butyl)-3-fluorochroman-4-one 1d. Following the described procedure, 340 mg of 6-(*tert*-butyl)chroman-4-one (1.53 mmol, 1.0 equiv) was used. Purification via flash column chromatography on silica gel (90:10 petroleum ether/ethyl acetate) yielded 240 mg of **1d** as a colorless oil (71%). ^1H NMR (400 MHz, chloroform-*d*) δ 7.90 (d, J = 2.5 Hz, 1H), 7.59 (dd, J = 8.8, 2.6 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 5.14 (ddd, J = 47.0, 9.2, 4.7 Hz, 1H), 4.66–4.45 (m, 2H), 1.31 (s, 9H). $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz,

chloroform-*d*) δ –203.87. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, chloroform-*d*) δ 187.6 (C–F, $^2J_{\text{CF}}$ = 15.2 Hz), 187.4 (C–F, $^2J_{\text{CF}}$ = 15.2 Hz), 159.4, 145.6, 134.8, 123.7, 118.8, 117.7, 86.8 (C–F, $^1J_{\text{CF}}$ = 188.9 Hz), 84.9 (C–F, $^1J_{\text{CF}}$ = 188.9 Hz), 69.0 (C–F, $^2J_{\text{CF}}$ = 26.3 Hz), 68.7 (C–F, $^2J_{\text{CF}}$ = 26.3 Hz), 34.5, 31.3. IR (solid) ν 2960, 2360, 1710 (C=O), 1697, 1614, 1489, 1086, 1043 cm^{-1} . HRMS (APCI) m/z [M + H]⁺ calcd for $\text{C}_{13}\text{H}_{15}\text{FO}_2$ 223.1129, found 223.1129.

3-Fluoro-6-phenoxychroman-4-one 1f. Following the described procedure, 300 mg of 8-phenoxychroman-4-one (1.25 mmol, 1.0 equiv) was used. Purification via flash column chromatography on silica gel (90:10 petroleum ether/EtOAc, then 100% dichloromethane) yielded 240 mg of **1f** as a colorless oil, which proceeded to solidify into a crystalline solid (71%). mp 66–68 °C. ^1H NMR (400 MHz, chloroform-*d*) δ 7.48 (d, J = 3.0 Hz, 1H), 7.38–7.31 (m, 2H), 7.27 (dd, J = 9.1, 2.9 Hz, 1H), 7.15–7.10 (m, 1H), 7.02 (d, J = 9.0 Hz, 1H), 6.99–6.94 (m, 2H), 5.14 (ddd, J = 46.9, 8.8, 4.7 Hz, 1H), 4.67–4.50 (m, 2H). $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, chloroform-*d*) δ –203.79. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, chloroform-*d*) δ 186.7 (C–F, $^2J_{\text{CF}}$ = 16.2 Hz), 186.6 (C–F, $^2J_{\text{CF}}$ = 16.2 Hz), 157.4, 157.1, 152.3, 130.1, 128.8, 123.8, 120.0, 119.6, 118.7, 116.0, 86.6 (C–F, $^1J_{\text{CF}}$ = 188.9 Hz), 84.7 (C–F, $^1J_{\text{CF}}$ = 188.9 Hz), 69.1 (C–F, $^2J_{\text{CF}}$ = 26.3 Hz), 68.9 (C–F, $^2J_{\text{CF}}$ = 26.3 Hz). IR (solid) ν 3064, 3015, 1700 (C=O), 1480, 1437, 1253, 1201, 1089 cm^{-1} . HRMS (APCI) m/z [M + H]⁺ calcd for $\text{C}_{15}\text{H}_{11}\text{FO}_3$ 259.0765, found 259.0765.

3,6-Difluorochroman-4-one 1g. Following the described procedure, 300 mg of 6-fluorochroman-4-one (1.8 mmol, 1.0 equiv) was used. Purification via flash column chromatography on silica gel (90:10 petroleum ether/ethyl acetate) yielded 294 mg of **1g** as a white crystalline solid (88%). mp 102–104 °C. ^1H NMR (400 MHz, chloroform-*d*) δ 7.56 (dd, J = 8.0, 3.2 Hz, 1H), 7.26 (ddd, J = 10.1, 7.6, 3.2 Hz, 1H), 7.01 (dd, J = 9.1, 4.1 Hz, 1H), 5.14 (ddd, J = 46.8, 8.8, 4.7 Hz, 1H), 4.70–4.49 (m, 2H). $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, chloroform-*d*) δ –119.99, –203.92. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, chloroform-*d*) δ 186.3 (C–F, $^2J_{\text{CF}}$ = 15.2 Hz), 186.1 (C–F, $^2J_{\text{CF}}$ = 15.2 Hz), 158.9 (C–F, $^1J_{\text{CF}}$ = 244.4 Hz), 157.5, 156.5 (C–F, $^1J_{\text{CF}}$ = 244.4 Hz), 124.6 (C–F, $^2J_{\text{CF}}$ = 25.3 Hz), 124.4 (C–F, $^2J_{\text{CF}}$ = 25.3 Hz), 120.0 (C–F, $^3J_{\text{CF}}$ = 6.1 Hz), 119.9 (C–F, $^3J_{\text{CF}}$ = 6.1 Hz), 119.8 (C–F, $^3J_{\text{CF}}$ = 7.1 Hz), 119.7 (C–F, $^3J_{\text{CF}}$ = 7.1 Hz), 112.6 (C–F, $^2J_{\text{CF}}$ = 24.2 Hz), 112.4 (C–F, $^2J_{\text{CF}}$ = 24.2 Hz), 86.3 (C–F, $^1J_{\text{CF}}$ = 188.9 Hz), 84.4 (C–F, $^1J_{\text{CF}}$ = 188.9 Hz), 69.0 (C–F, $^2J_{\text{CF}}$ = 25.2 Hz), 68.8 (C–F, $^2J_{\text{CF}}$ = 25.2 Hz). IR (solid) ν 2987, 2900, 2360, 2339, 1483, 1076, 1058 cm^{-1} . The data are in accordance with those previously reported in the literature.^{12b}

3,7-Difluorochroman-4-one 1h. Following the described procedure, 300 mg of 7-fluorochroman-4-one (1.8 mmol, 1.0 equiv) was used. Purification via flash column chromatography on silica gel (90:10 petroleum ether/ethyl acetate) yielded 275 mg of **1h** as a white crystalline solid (83%). mp 52–54 °C. ^1H NMR (400 MHz, chloroform-*d*) δ 7.94 (ddd, J = 7.9, 6.1, 1.9 Hz, 1H), 6.87–6.77 (m, 1H), 6.70 (dt, J = 9.7, 1.9 Hz, 1H), 5.12 (ddd, J = 46.9, 8.3, 4.7 Hz, 1H), 4.70–4.52 (m, 2H). $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, chloroform-*d*) δ –98.54, –203.54. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, chloroform-*d*) δ 185.6 (C–F, $^2J_{\text{CF}}$ = 16.2 Hz), 185.5 (C–F, $^2J_{\text{CF}}$ = 16.2 Hz), 169.3 (C–F, $^1J_{\text{CF}}$ = 258.6 Hz), 166.8 (C–F, $^1J_{\text{CF}}$ = 258.6 Hz), 163.1 (C–F, $^3J_{\text{CF}}$ = 14.1 Hz), 163.0 (C–F, $^3J_{\text{CF}}$ = 14.1 Hz), 130.5 (C–F, $^3J_{\text{CF}}$ = 12.1 Hz), 130.4 (C–F, $^3J_{\text{CF}}$ = 12.1 Hz), 116.4, 111.3 (C–F, $^2J_{\text{CF}}$ = 23.2 Hz), 111.0 (C–F, $^2J_{\text{CF}}$ = 23.2 Hz), 105.1 (C–F, $^2J_{\text{CF}}$ = 25.3 Hz), 104.9 (C–F, $^2J_{\text{CF}}$ = 25.3 Hz), 86.2 (C–F, $^1J_{\text{CF}}$ = 187.9 Hz), 84.4 (C–F, $^1J_{\text{CF}}$ = 187.9 Hz), 69.4 (C–F, $^2J_{\text{CF}}$ = 26.3 Hz), 69.1 (C–F, $^2J_{\text{CF}}$ = 26.3 Hz). IR (solid) ν 2987, 2900, 2360, 2339, 1483, 1076, 1058 cm^{-1} . HRMS (APCI) m/z [M + H]⁺ calcd for $\text{C}_9\text{H}_6\text{F}_2\text{O}_2$ 185.0409, found 185.0408.

7-Bromo-3-fluorochroman-4-one 1i. Following the described procedure, 300 mg of 7-bromochroman-4-one (1.3 mmol, 1.0 equiv) was used. Purification via flash column chromatography on silica gel (95:5 petroleum ether/ethyl acetate) yielded 248 mg of **1i** as a white solid (77%). mp 118–120 °C. ^1H NMR (400 MHz, chloroform-*d*) δ 7.78 (d, J = 8.8 Hz, 1H), 7.28–7.21 (m, 2H), 5.13 (ddd, J = 46.9, 8.7, 4.7 Hz, 1H), 4.72–4.47 (m, 2H). $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, chloroform-*d*) δ –203.53. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz,

chloroform-*d*) δ 186.3 (C–F, $^2J_{CF}$ = 16.2 Hz), 186.1 (C–F, $^2J_{CF}$ = 16.2 Hz), 161.4, 131.7, 129.0, 126.3, 121.3, 118.5, 86.3 (C–F, $^1J_{CF}$ = 188.9 Hz), 84.4 (C–F, $^1J_{CF}$ = 188.9 Hz), 69.2 (C–F, $^2J_{CF}$ = 26.3 Hz), 68.9 (C–F, $^2J_{CF}$ = 26.3 Hz). IR (solid) ν 2987, 2900, 2360, 2339, 1483, 1076, 1058 cm^{-1} . HRMS (APCI) m/z [M + H]⁺ calcd for C₉H₆BrFO₂H 244.9608, found 244.9609.

3-Fluoro-6-nitrochroman-4-one 1j. Following the described procedure, 300 mg of 6-nitro-chroman-4-one (1.55 mmol, 1.0 equiv) was used. Purification via flash column chromatography on silica gel (85:15 petroleum ether/ethyl acetate and 70:30 CH₂Cl₂/petroleum ether) yielded 59 mg of **1j** as a pale yellow solid (18%). mp 120–122 °C. ¹H NMR (400 MHz, chloroform-*d*) δ 8.80 (d, J = 2.8 Hz, 1H), 8.39 (dd, J = 9.2, 2.9 Hz, 1H), 7.18 (d, J = 9.2 Hz, 1H), 5.28–5.10 (m, 1H), 4.79–4.68 (m, 2H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –202.73. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 185.0 (C–F, $^2J_{CF}$ = 16.2 Hz), 184.8 (C–F, $^2J_{CF}$ = 16.2 Hz), 164.9, 149.5, 131.2, 124.4, 122.9, 119.5, 85.8 (C–F, $^1J_{CF}$ = 189.9 Hz), 83.9 (C–F, $^1J_{CF}$ = 189.9 Hz), 69.5 (C–F, $^2J_{CF}$ = 25.3 Hz), 69.2 (C–F, $^2J_{CF}$ = 25.3 Hz). IR (solid) ν 2987, 2900, 2360, 2339, 1483, 1076, 1058 cm^{-1} . HRMS (APCI) m/z [M + H]⁺ calcd for C₉H₆FNO₄H 212.0354, found 212.0354.

8-Chloro-3-fluoro-5-methylchroman-4-one 1k. Following the described procedure, 250 mg of 8-chloro-5-methylchroman-4-one (1.27 mmol, 1.0 equiv) was used. Purification via flash column chromatography on silica gel (95:5 petroleum ether/ethyl acetate) yielded 140 mg of **1k** as a white solid (51%). mp 86–88 °C. ¹H NMR (400 MHz, chloroform-*d*) δ 7.46 (d, J = 8.0 Hz, 1H), 6.83 (dd, J = 8.1, 1.0 Hz, 1H), 5.11 (ddd, J = 47.4, 9.0, 4.6 Hz, 1H), 4.81–4.52 (m, 2H), 2.62 (s, 3H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –202.78. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 188.0 (C–F, $^2J_{CF}$ = 16.1 Hz), 187.9 (C–F, $^2J_{CF}$ = 16.1 Hz), 157.3, 141.8, 135.7, 125.5, 120.4, 119.1, 86.6 (C–F, $^1J_{CF}$ = 188.9 Hz), 84.7 (C–F, $^1J_{CF}$ = 188.9 Hz), 68.8 (C–F, $^2J_{CF}$ = 26.3 Hz), 68.5 (C–F, $^2J_{CF}$ = 26.3 Hz), 22.4. IR (solid) ν 2930, 2360, 2341, 1699 (C=O), 1474, 1068, 1027 cm^{-1} . HRMS (APCI) m/z [M + H]⁺ calcd for C₁₀H₈ClFO₂H 215.0270, found 215.0270.

6-Methoxy-3-fluorochroman-4-one 1e. To a 25 mL-round-bottom flask fitted with a stirrer and a condenser and set under argon were added 6-methoxy-chroman-4-one (300 mg, 1.7 mmol, 1.0 equiv), NFSI (1.34 g, 4.3 mmol, 2.5 equiv), and MeOH (8 mL). The resulting mixture was heated at reflux (oil bath) for 24 h (monitored by silica gel TLC, petroleum ether/EtOAc 8:2). After the completion of the reaction, the medium was cooled, and the methanol was evaporated under reduced pressure. The residue was then diluted with CH₂Cl₂ (10 mL) and washed with a 2 M HCl aqueous solution (8 mL). The organic layer was then washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude was purified via flash column chromatography on silica gel (45:45:10 petroleum ether/toluene/MTBE, then 90:10 petroleum ether/ethyl acetate) to yield 176 mg of **1e** as a white crystalline solid (53%). mp 90–92 °C. ¹H NMR (400 MHz, chloroform-*d*) δ 7.31 (d, J = 3.2 Hz, 1H), 7.14 (dd, J = 9.1, 3.2 Hz, 1H), 6.97–6.92 (m, 1H), 5.14 (ddd, J = 47.0, 9.0, 4.7 Hz, 1H), 4.65–4.45 (m, 2H), 3.81 (s, 3H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –203.84. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 187.3 (C–F, $^2J_{CF}$ = 16.2 Hz), 187.1 (C–F, $^2J_{CF}$ = 16.2 Hz), 156.2, 154.9, 126.4, 119.4, 107.7, 86.7 (C–F, $^1J_{CF}$ = 188.9 Hz), 84.9 (C–F, $^1J_{CF}$ = 188.9 Hz), 69.1 (C–F, $^2J_{CF}$ = 26.3 Hz), 68.9 (C–F, $^2J_{CF}$ = 26.3 Hz), 56.0. IR (solid) ν 3012, 2945, 2360, 1692 (C=O), 1613, 1433, 1275, 1034, 1015 cm^{-1} . HRMS (APCI) m/z [M + H]⁺ calcd for C₁₀H₈FO₃H 197.0608, found 197.0609.

3,6-Difluorothiochroman-4-one 1l. To a 0 °C solution of LiHMDS (1.0 M, 1.05 equiv) in THF in a round-bottom tube set under argon was slowly added a solution of 6-fluorothiochroman-4-one (350 mg, 1.92 mmol, 1.0 equiv) in THF (2 mL) over 5 min. The mixture was stirred at 0 °C for 2 h. The resulting solution was then added dropwise over 5 min via a cannula to a –78 °C solution of NFSI (1.1 equiv) in THF (4 mL). The reaction mixture was allowed to come to room temperature overnight. The reaction mixture was diluted with 3 mL of CH₂Cl₂, quenched with 5 mL of a saturated NH₄Cl aqueous solution, and extracted with CH₂Cl₂ (3 × 10 mL).

The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification via flash column chromatography on silica gel (95:5 petroleum ether/acetone eluent) yielded 100 mg of **1l** as a pale yellow solid (26%). mp 143–145 °C. ¹H NMR (400 MHz, chloroform-*d*) δ 7.80 (dd, J = 9.0, 2.9 Hz, 1H), 7.28–7.23 (m, 1H), 7.19 (ddd, J = 8.7, 7.5, 2.9 Hz, 1H), 5.42 (ddd, J = 47.4, 13.4, 4.8 Hz, 1H), 3.61 (ddd, J = 13.4, 12.6, 3.0 Hz, 1H), 3.29 (ddd, J = 12.6, 9.4, 4.8 Hz, 1H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –115.45, –184.62. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 189.1 (C–F, $^2J_{CF}$ = 16.2 Hz), 188.9 (C–F, $^2J_{CF}$ = 16.2 Hz), 162.2 (C–F, $^1J_{CF}$ = 248 Hz), 159.7 (C–F, $^1J_{CF}$ = 248 Hz), 136.0 (C–F, $^4J_{CF}$ = 2.0 Hz), 135.9 (C–F, $^4J_{CF}$ = 2.0 Hz), 131.9 (C–F, $^3J_{CF}$ = 6.1 Hz), 131.9 (C–F, $^3J_{CF}$ = 6.1 Hz), 129.2 (C–F, $^3J_{CF}$ = 7.1 Hz), 129.2 (C–F, $^3J_{CF}$ = 7.1 Hz), 122.3 (C–F, $^2J_{CF}$ = 23.2 Hz), 122.1 (C–F, $^2J_{CF}$ = 23.2 Hz), 116.2 (C–F, $^2J_{CF}$ = 23.2 Hz), 115.9 (C–F, $^2J_{CF}$ = 23.2 Hz), 90.5 (C–F, $^1J_{CF}$ = 198.0 Hz), 88.5 (C–F, $^1J_{CF}$ = 198.0 Hz), 31.3 (C–F, $^2J_{CF}$ = 23.2 Hz), 31.1 (C–F, $^2J_{CF}$ = 23.2 Hz). IR (solid) ν 2987, 2911, 2359, 2340, 1684 (C=O), 1406, 1051 cm^{-1} . HRMS (APCI) m/z [M + H]⁺ calcd for C₉H₆F₂OSH 201.0180, found 201.0180.

General Procedure for the Asymmetric Transfer Hydrogenation of 3-Fluorochroman-4-ones. In a round-bottom tube charged with the corresponding 3-fluoro-4-chromanone (0.60 mmol; 1.0 equiv) set under argon was added 1.0 mL of a solution of (*R,R*)-**A** in acetonitrile (0.76 mg/mL, 1.2 μ mol, 0.002 equiv). The mixture was stirred for 1 min before adding 0.52 mL of a formic acid/triethylamine (1:1) mixture (3.60 mmol; 6.0 equiv) by syringe. The reaction mixture was stirred at 40 °C (oil bath) for 6 h and then quenched with 3 mL of a saturated NaHCO₃ aqueous solution. The media was extracted with CH₂Cl₂ (2 × 4 mL), and the organic layers dried over MgSO₄, filtered, and concentrated under vacuum. The diastereoisomeric ratio was determined by ¹H NMR analysis of the crude product. The product was purified with a flash column chromatography on silica gel (petroleum ether/EtOAc) and the enantiomeric excess was determined by SFC analysis (CHIRALPAK IE column).

(3*R*,4*S*)-3-Fluorochroman-4-ol 2a. Used 100 mg of 3-fluorochroman-4-one (0.60 mmol; 1.0 equiv). Yielded 97 mg of a white fluffy solid (95% yield), flash column with a petroleum ether/ethyl acetate eluent (gradient from 90:10 to 70:30). mp 164–166 °C. dr (*cis/trans*) = 99:1, ee_{cis} > 99%. [α]_D²⁰ = –35.6 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 7.48 (dt, J = 7.8, 1.2 Hz, 1H), 7.26–7.20 (m, 1H), 7.00 (td, J = 7.5, 1.2 Hz, 1H), 6.86 (dd, J = 8.2, 1.1 Hz, 1H), 5.11–4.85 (m, 2H), 4.48 (ddd, J = 12.2, 7.8, 5.6 Hz, 1H), 4.22 (ddd, J = 28.4, 12.2, 2.0 Hz, 1H), 2.28 (d, J = 6.9 Hz, 1H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –209.43. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 153.5, 130.0, 129.0, 121.8, 121.6, 116.5, 87.2 (C–F, $^1J_{CF}$ = 178.8 Hz), 85.4 (C–F, $^1J_{CF}$ = 178.8 Hz), 65.4 (C–F, $^2J_{CF}$ = 20.2 Hz), 65.2 (C–F, $^2J_{CF}$ = 20.2 Hz), 64.6 (C–F, $^2J_{CF}$ = 22.2 Hz), 64.4 (C–F, $^2J_{CF}$ = 22.2 Hz). IR (solid) ν 3285 (br, OH), 1583, 1485, 1466, 1224, 1053, 987 cm^{-1} . HRMS (APCI) m/z [M]⁺ calcd for C₉H₈FO₂ 168.0581, found 168.0581. SFC: Chiralpak IE, scCO₂/MeOH 90:10, 2.0 mL/min, P = 100 bar, λ = 215 nm, t_R [*trans*] = 3.49 min, t_R [*cis*] = 3.73 min, t_R [*cis*-(3*R*,4*S*)] = 4.76 min (major), t_R [*cis*-(3*S*,4*R*)] = 5.78 min.

(3*R*,4*S*)-6-Methyl-3-fluorochroman-4-ol 2b. Used 108 mg of 3-fluoro-6-methylchroman-4-one (0.60 mmol; 1.0 equiv). Yielded 101 mg of a white solid (92% yield), flash column with a petroleum ether/ethyl acetate eluent (gradient from 90:10 to 70:30). mp 184–186 °C. dr (*cis/trans*) = 98:2, ee_{cis} = 98%. [α]_D²⁰ = –40.7 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 7.34–7.16 (m, 1H), 7.03 (ddt, J = 8.3, 2.2, 0.7 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 4.98 (ddd, J = 48.2, 5.8, 3.6 Hz, 1H), 4.90–4.78 (m, 1H), 4.44 (ddd, J = 12.2, 7.6, 5.8 Hz, 1H), 4.18 (ddd, J = 27.7, 12.2, 2.1 Hz, 1H), 2.37–2.23 (m, 4H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –209.45. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 151.3, 131.0, 130.7, 129.2, 121.4, 116.2, 87.4 (C–F, $^1J_{CF}$ = 178.8 Hz), 85.6 (C–F, $^1J_{CF}$ = 178.8 Hz), 65.4 (C–F, $^2J_{CF}$ = 20.2 Hz), 65.2 (C–F, $^2J_{CF}$ = 20.2 Hz), 64.5 (C–F, $^2J_{CF}$ = 23.2 Hz), 64.3 (C–F, $^2J_{CF}$ = 23.2 Hz), 20.7. IR (solid) ν 3251 (br, OH), 1493, 1245, 1237, 1153, 1107, 1057 cm^{-1} . HRMS (APCI) m/z [M + H]⁺ calcd for C₁₀H₁₁FO₂H 182.0738, found 182.0737. SFC:

Chiralpak IE, *sc* CO₂/MeOH 93:7, 2.0 mL/min, *P* = 100 bar, λ = 215 nm, t_R [*cis*-(3*R*,4*S*)] = 5.49 min (major), t_R [*cis*-(3*S*,4*R*)] = 7.97 min.

(3*R*,4*S*)-3-Fluoro-8-methylchroman-4-ol 2c. Used 108 mg of 3-fluoro-8-methylchroman-4-one (0.60 mmol; 1.0 equiv). Yielded 104 mg of a white fluffy solid (95% yield), flash column with a petroleum ether/ethyl acetate eluent (gradient from 90:10 to 70:30). mp 188–190 °C. dr (*cis/trans*) = 99:1, ee_{cis} = 98%. [α]_D²⁰ = –19.5 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 7.31 (ddt, *J* = 7.7, 1.6, 0.7 Hz, 1H), 7.09 (ddt, *J* = 7.4, 1.7, 0.8 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 5.11–4.85 (m, 2H), 4.51 (ddd, *J* = 12.2, 7.7, 5.8 Hz, 1H), 4.24 (ddd, *J* = 27.5, 12.2, 2.2 Hz, 1H), 2.27 (d, *J* = 8.6 Hz, 1H), 2.20 (s, 3H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –209.36. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 151.6, 131.1, 126.5, 125.8, 121.3, 121.1, 87.3 (C–F, ¹*J*_{CF} = 178.8 Hz), 85.5 (C–F, ¹*J*_{CF} = 178.8 Hz), 65.5 (C–F, ²*J*_{CF} = 20.2 Hz), 65.3 (C–F, ²*J*_{CF} = 20.2 Hz), 64.5 (C–F, ²*J*_{CF} = 22.2 Hz), 64.3 (C–F, ²*J*_{CF} = 22.2 Hz), 16.1. IR (solid) ν 3254 (br, OH), 1469, 1344, 1266, 1210, 1091, 1066 cm^{–1}. HRMS (APCI) *m/z* [*M* + *H*]⁺ calcd for C₁₀H₁₁FO₂H 182.0738, found 182.0737. SFC: Chiralpak IE, *sc* CO₂/MeOH 93:7, 1.0 mL/min, *P* = 100 bar, λ = 215 nm, t_R [*cis*-(3*R*,4*S*)] = 5.35 min (major), t_R [*cis*-(3*S*,4*R*)] = 5.84 min.

(3*R*,4*S*)-6-(*tert*-Butyl)-3-fluorochroman-4-ol 2d. Used 100 mg of 6-(*tert*-butyl)-3-fluorochroman-4-one (0.45 mmol; 1.0 equiv). Yielded 81 mg of a white solid (80% yield), flash column with a petroleum ether/ethyl acetate eluent (gradient from 90:10 to 70:30). mp 66–68 °C. dr (*cis/trans*) = 98:2, ee_{cis} = 98%. [α]_D²⁰ = –44.6 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 7.47 (dd, *J* = 2.5, 0.9 Hz, 1H), 7.30–7.22 (m, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 5.12–4.81 (m, 2H), 4.44 (ddd, *J* = 12.0, 7.5, 5.8 Hz, 1H), 4.18 (ddd, *J* = 27.7, 12.2, 2.1 Hz, 1H), 2.42 (d, *J* = 8.7 Hz, 1H), 1.31 (s, 9H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –209.26. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 151.2, 144.5, 127.3, 125.6, 120.9, 116.0, 87.4 (C–F, ¹*J*_{CF} = 178.8 Hz), 85.7 (C–F, ¹*J*_{CF} = 178.8 Hz), 65.6 (C–F, ²*J*_{CF} = 19.2 Hz), 65.4 (C–F, ²*J*_{CF} = 19.2 Hz), 64.5 (C–F, ²*J*_{CF} = 23.2 Hz), 64.3 (C–F, ²*J*_{CF} = 23.2 Hz), 34.4, 31.6. IR (solid) ν 3340 (br, OH), 2960, 1494, 1265, 1232, 1109, 1058 cm^{–1}. HRMS (APCI) *m/z* [*M*]⁺ calcd for C₁₃H₁₇FO₂ 224.1207, found 224.1209. SFC: Chiralpak IE, *sc* CO₂/MeOH 93:7, 2.0 mL/min, *P* = 100 bar, λ = 215 nm, t_R [*cis*-(3*R*,4*S*)] = 3.96 min (major), t_R [*cis*-(3*S*,4*R*)] = 5.09 min.

(3*R*,4*S*)-3-Fluoro-6-methoxychroman-4-ol 2e. Used 118 mg of 3,6-difluorochroman-4-one (0.60 mmol; 1.0 equiv). Yielded 111 mg of a white fluffy solid (93% yield), flash column with a petroleum ether/ethyl acetate eluent (gradient from 90:10 to 70:30). mp 156–158 °C. dr (*cis/trans*) = 99:1, ee_{cis} = 99%. [α]_D²⁰ = –38.3 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 7.01 (dt, *J* = 2.6, 0.9 Hz, 1H), 6.85–6.74 (m, 2H), 5.10–4.80 (m, 2H), 4.45 (ddd, *J* = 12.4, 8.1, 5.3 Hz, 1H), 4.23–4.08 (m, 1H), 3.78 (s, 3H), 2.32 (dd, *J* = 9.4, 2.4 Hz, 1H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –209.72. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 154.4, 147.4, 122.3, 117.3, 116.7, 112.5, 87.2 (C–F, ¹*J*_{CF} = 178.8 Hz), 85.5 (C–F, ¹*J*_{CF} = 178.8 Hz), 65.6 (C–F, ²*J*_{CF} = 20.2 Hz), 65.4 (C–F, ²*J*_{CF} = 20.2 Hz), 64.88 (C–F, ²*J*_{CF} = 22.2 Hz), 64.7 (C–F, ²*J*_{CF} = 22.2 Hz), 55.9. IR (solid) ν 3221 (br, OH), 2921, 1491, 1210, 1158, 1105, 1034 cm^{–1}. HRMS (APCI) *m/z* [*M* + *H* – H₂O]⁺ calcd for C₁₀H₉FO₂H 181.0664, found 181.0659. SFC: Chiralpak IE, *sc* CO₂/MeOH 90:10, 2.0 mL/min, *P* = 100 bar, λ = 215 nm, t_R [*trans*] = 4.44 min, t_R [*trans*] = 5.47 min, t_R [*cis*-(3*R*,4*S*)] = 7.56 min (major), t_R [*cis*-(3*S*,4*R*)] = 9.48 min.

(3*R*,4*S*)-3-Fluoro-6-phenoxychroman-4-ol 2f. Used 100 mg of 6-phenoxychroman-4-one (0.39 mmol; 1.0 equiv). Yielded 98 mg of a white fluffy solid (96% yield), flash column with a petroleum ether/ethyl acetate eluent (70:30). mp 155–157 °C. dr (*cis/trans*) = 98:2, ee_{cis} = 92%. [α]_D²⁰ = –47.2 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 7.35–7.28 (m, 2H), 7.17 (dd, *J* = 2.9, 0.9 Hz, 1H), 7.11–7.02 (m, 1H), 7.00–6.88 (m, 3H), 6.84 (d, *J* = 8.9 Hz, 1H), 5.13–4.79 (m, 2H), 4.49 (ddd, *J* = 12.4, 8.3, 5.2 Hz, 1H), 4.21 (ddd, *J* = 30.5, 12.4, 1.8 Hz, 1H), 2.26 (d, *J* = 9.4 Hz, 1H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –209.66. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 158.2, 151.1, 149.5, 129.8, 123.0, 122.9, 121.5, 119.3, 118.1, 117.6, 87.0 (C–F, ¹*J*_{CF} = 178.8 Hz), 85.3 (C–F, ¹*J*_{CF} = 178.8

Hz), 65.4 (C–F, ²*J*_{CF} = 19.1 Hz), 65.2 (C–F, ²*J*_{CF} = 19.1 Hz), 65.0 (C–F, ²*J*_{CF} = 22.2 Hz), 64.8 (C–F, ²*J*_{CF} = 22.2 Hz). IR (solid) ν 3232 (br, OH), 1483, 1255, 1204, 1108, 1077 cm^{–1}. HRMS (APCI) *m/z* [*M*]⁺ calcd for C₁₅H₁₃FO₃ 260.0843, found 260.0842. SFC: Chiralpak IE, *sc* CO₂/MeOH 85:15, 2.0 mL/min, *P* = 100 bar, λ = 215 nm, t_R [*cis*-(3*S*,4*R*)] = 9.00 min, t_R [*trans*] = 10.47 min, t_R [*trans*] = 12.50 min, t_R [*cis*-(3*R*,4*S*)] = 14.00 min (major).

(3*R*,4*S*)-3,6-Difluorochroman-4-ol 2g. Used 110 mg of 3,6-difluorochroman-4-one (0.60 mmol; 1.0 equiv). Yielded 104 mg of a white fluffy solid (93% yield), flash column with a petroleum ether/ethyl acetate eluent (gradient from 90:10 to 70:30). mp 173–175 °C. dr (*cis/trans*) = 98:2, ee_{cis} = 99%. [α]_D²⁰ = –45.9 (c 1.0, MeOH). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.23–7.10 (m, 1H), 7.05–6.94 (m, 1H), 6.78 (dd, *J* = 8.9, 4.7 Hz, 1H), 5.93 (d, *J* = 7.0 Hz, 1H), 5.11–4.91 (m, 1H), 4.85 (ddd, *J* = 28.0, 7.2, 3.1 Hz, 1H), 4.45–4.17 (m, 2H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –118.71, –202.41. ¹³C{¹H} NMR (101 MHz, DMSO-*d*₆) δ 206.8, 157.6 (C–F, ¹*J*_{CF} = 237.4 Hz), 155.3 (C–F, ¹*J*_{CF} = 237.4 Hz), 149.1, 125.5 (C–F, ³*J*_{CF} = 7.1 Hz), 125.4 (C–F, ³*J*_{CF} = 7.1 Hz), 116.6 (C–F, ³*J*_{CF} = 8.1 Hz), 116.5 (C–F, ³*J*_{CF} = 8.1 Hz), 115.2 (C–F, ²*J*_{CF} = 24.2 Hz), 115.0 (C–F, ²*J*_{CF} = 24.2 Hz), 113.7 (C–F, ²*J*_{CF} = 24.2 Hz), 113.5 (C–F, ²*J*_{CF} = 24.2 Hz), 86.7 (C–F, ¹*J*_{CF} = 178.8 Hz), 85.0 (C–F, ¹*J*_{CF} = 178.8 Hz), 65.9 (C–F, ²*J*_{CF} = 19.2 Hz), 65.7 (C–F, ²*J*_{CF} = 19.2 Hz), 63.7 (C–F, ²*J*_{CF} = 19.2 Hz), 63.5 (C–F, ²*J*_{CF} = 19.2 Hz). IR (solid) ν 3275 (br, OH), 1486, 1246, 1203, 1144, 1104, 1075, 1051 cm^{–1}. HRMS (APCI) *m/z* [*M* + *H*]⁺ calcd for C₉H₈F₂O₂H 186.0487, found 186.0487. SFC: Chiralpak IE, *sc* CO₂/MeOH 95:5, 2.0 mL/min, *P* = 100 bar, λ = 215 nm, t_R [*cis*-(3*S*,4*R*)] = 6.28 min, t_R [*cis*-(3*R*,4*S*)] = 7.74 min (major).

(3*R*,4*S*)-3,7-Difluorochroman-4-ol 2h. Used 110 mg of 3,7-difluorochroman-4-one (0.60 mmol; 1.0 equiv). Yielded 105 mg of a white fluffy solid (95% yield), flash column with a petroleum ether/ethyl acetate eluent (gradient from 90:10 to 70:30). mp 158–160 °C. dr (*cis/trans*) = 98:2, ee_{cis} = 98%. [α]_D²⁰ = –47.1 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 7.42 (ddd, *J* = 8.6, 6.5, 0.9 Hz, 1H), 6.71 (td, *J* = 8.4, 2.5 Hz, 1H), 6.57 (dd, *J* = 10.0, 2.5 Hz, 1H), 4.99 (dtd, *J* = 48.1, 3.6, 1.8 Hz, 1H), 4.89–4.78 (m, 1H), 4.48 (ddd, *J* = 12.3, 7.9, 5.6 Hz, 1H), 4.22 (ddd, *J* = 28.2, 12.3, 2.1 Hz, 1H), 2.29 (dd, *J* = 8.8, 2.4 Hz, 1H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –111.51, –209.65. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 164.8 (C–F, ¹*J*_{CF} = 247.5 Hz), 162.4 (C–F, ¹*J*_{CF} = 247.5 Hz), 154.7 (C–F, ³*J*_{CF} = 13.1 Hz), 154.6 (C–F, ³*J*_{CF} = 13.1 Hz), 130.4 (C–F, ³*J*_{CF} = 10.1 Hz), 130.3 (C–F, ³*J*_{CF} = 10.1 Hz), 117.8, 109.2 (C–F, ²*J*_{CF} = 22.2 Hz), 109.0 (C–F, ²*J*_{CF} = 22.2 Hz), 103.8 (C–F, ²*J*_{CF} = 24.2 Hz), 103.5 (C–F, ²*J*_{CF} = 24.2 Hz), 86.98 (C–F, ¹*J*_{CF} = 178.8 Hz), 85.2 (C–F, ¹*J*_{CF} = 178.8 Hz), 65.0 (C–F, ²*J*_{CF} = 15.2 Hz), 64.9 (C–F, ²*J*_{CF} = 15.2 Hz), 64.8 (C–F, ²*J*_{CF} = 18.2 Hz), 64.6 (C–F, ²*J*_{CF} = 18.2 Hz). IR (solid) ν 3338 (br, OH), 1596, 1502, 1262, 1155, 1101, 1053 cm^{–1}. HRMS (APCI) *m/z* [*M* + *H*]⁺ calcd for C₉H₈F₂O₂H 186.0487, found 186.0487. SFC: Chiralpak IE, *sc* CO₂/MeOH 85:15, 2.0 mL/min, *P* = 100 bar, λ = 215 nm, t_R [*cis*-(3*R*,4*S*)] = 4.59 min (major), t_R [*trans*] = 5.13 min, t_R [*trans*] = 5.28 min, t_R [*cis*-(3*S*,4*R*)] = 6.64 min.

(3*R*,4*S*)-7-Bromo-3-fluorochroman-4-ol 2i. Used 147 mg of 7-bromo-3-fluorochroman-4-one (0.60 mmol; 1.0 equiv). Yielded 138 mg of a white fluffy solid (93% yield), flash column with a petroleum ether/ethyl acetate eluent (75:25). mp 165–167 °C. dr (*cis/trans*) = 99:1, ee_{cis} = 99%. [α]_D²⁰ = –36.5 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 7.34 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.12 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 5.00 (ddd, *J* = 48.2, 5.3, 3.6 Hz, 1H), 4.84 (ddd, *J* = 20.6, 9.3, 3.6 Hz, 1H), 4.49 (ddd, *J* = 12.4, 8.3, 5.2 Hz, 1H), 4.21 (ddd, *J* = 30.1, 12.5, 1.9 Hz, 1H), 2.28 (dd, *J* = 9.3, 2.4 Hz, 1H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ –209.57. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 154.2, 130.1, 124.9, 123.1, 121.0, 119.6, 86.8 (C–F, ¹*J*_{CF} = 179.8 Hz), 85.0 (C–F, ¹*J*_{CF} = 179.8 Hz), 65.1, 65.1 (C–F, ²*J*_{CF} = 19.1 Hz), 64.9 (C–F, ²*J*_{CF} = 19.1 Hz). IR (solid) ν 3233 (br, OH), 1601, 1480, 1410, 1225, 1106, 1068, 1061 cm^{–1}. HRMS (APCI) *m/z* [*M*]⁺ calcd for C₉H₈BrFO₂ 245.9686, found 245.9685. SFC: Chiralpak IE, *sc* CO₂/MeOH

80:20, 2.0 mL/min, $P = 100$ bar, $\lambda = 215$ nm, t_R [*cis*-(3*R*,4*S*)] = 4.27 min (major), t_R [*cis*-(3*S*,4*R*)] = 6.07 min.

(3*R*,4*S*)-3-Fluoro-6-nitrochroman-4-ol 2j. Used 50 mg of 6-nitro-3-fluorochroman-4-one (0.24 mmol; 1.0 equiv). Yielded 46 mg of a white solid (92% yield), flash column with a petroleum ether/ethyl acetate eluent (gradient from 90:10 to 60:40). mp 150–152 °C. dr (*cis/trans*) = 98:2, ee_{cis} = 98%. [α]_D²⁰ = −114.6 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 8.47 (dd, $J = 2.7, 1.1$ Hz, 1H), 8.12 (ddd, $J = 9.1, 2.8, 0.6$ Hz, 1H), 6.94 (d, $J = 9.1$ Hz, 1H), 5.09 (dt, $J = 48.3, 4.3, 3.4$ Hz, 1H), 4.94 (ddd, $J = 22.3, 9.7, 3.3$ Hz, 1H), 4.64 (ddd, $J = 12.9, 9.5, 4.3$ Hz, 1H), 4.34 (ddt, $J = 33.5, 13.0, 1.4$ Hz, 1H), 2.42 (d, $J = 10.0$ Hz, 1H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ −209.36. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 158.5, 142.3, 125.7, 125.2, 122.8, 117.2, 86.2 (C–F, ¹ $J_{CF} = 179.8$ Hz), 84.4 (C–F, ¹ $J_{CF} = 179.8$ Hz), 66.2 (C–F, ² $J_{CF} = 22.2$ Hz), 65.9 (C–F, ² $J_{CF} = 22.2$ Hz), 65.0 (C–F, ² $J_{CF} = 20.2$ Hz), 64.8 (C–F, ² $J_{CF} = 20.2$ Hz). IR (solid) ν 3268 (br, OH), 2923, 1514, 1476, 1336, 1253, 1101, 1058 cm^{−1}. HRMS (APCI) m/z [M + H]⁺ calcd for C₉H₈FN₂O₄H 214.0510, found 214.0511. SFC: Chiralpak IE, sc CO₂/MeOH 85:15, 2.0 mL/min, $P = 100$ bar, $\lambda = 215$ nm, t_R [*cis*-(3*S*,4*R*)] = 8.94 min, t_R [*cis*-(3*R*,4*S*)] = 14.10 min (major).

(3*R*,4*S*)-8-Chloro-3-fluoro-5-methylchroman-4-ol 2k. Used 100 mg of 8-chloro-3-fluoro-5-methylchroman-4-one (0.47 mmol; 1.0 equiv). Yielded 98 mg of a white solid (96% yield), flash column with a petroleum ether/ethyl acetate eluent (75:25). mp 136–138 °C. dr (*cis/trans*) = 98:2, ee_{cis} = 99%. [α]_D²⁰ = +100.5 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 7.23 (d, $J = 8.1$ Hz, 1H), 6.77 (dt, $J = 8.1, 0.7$ Hz, 1H), 5.10–4.87 (m, 2H), 4.40–4.30 (m, 2H), 2.42 (s, 3H), 2.39 (s, 1H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ −208.42. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 149.8, 138.7, 130.5, 123.8, 120.7, 119.3, 87.7 (C–F, ¹ $J_{CF} = 179.8$ Hz), 85.9 (C–F, ¹ $J_{CF} = 179.8$ Hz), 62.7 (C–F, ² $J_{CF} = 19.2$ Hz), 62.5 (C–F, ² $J_{CF} = 19.2$ Hz), 61.7 (C–F, ² $J_{CF} = 29.3$ Hz), 61.4 (C–F, ² $J_{CF} = 29.3$ Hz), 18.4. IR (solid) ν 3275 (br, OH), 1420, 1263, 1229, 1193, 1096, 1075 cm^{−1}. HRMS (APCI) m/z [M]⁺ calcd for C₁₀H₁₀ClFO₂ 216.0348, found 216.0348. SFC: Chiralpak IE, sc CO₂/MeOH 93:7, 2.0 mL/min, $P = 100$ bar, $\lambda = 215$ nm, t_R [*cis*-(3*R*,4*S*)] = 5.56 min (major), t_R [*cis*-(3*S*,4*R*)] = 11.82 min.

(3*S*,4*S*)-3,6-Difluorothiochroman-4-ol 2l. Used 56 mg of 3,6-difluorothiochroman-4-one (0.47 mmol; 1.0 equiv). Yielded 45 mg of a white solid (80% yield), flash column with a petroleum ether/ethyl acetate eluent (90:10). mp 158–160 °C. dr (*cis/trans*) = 92:8, ee_{cis} = 99%. [α]_D²⁰ = +108 (c 1.0, CHCl₃). ¹H NMR (400 MHz, chloroform-*d*) δ 7.21–7.14 (m, 1H), 7.12 (dd, $J = 8.7, 5.2$ Hz, 1H), 7.00–6.90 (m, 1H), 5.19 (ddd, $J = 48.6, 9.1, 4.0$ Hz, 1H), 4.80 (ddd, $J = 15.7, 5.8, 2.9$ Hz, 1H), 3.49 (ddd, $J = 12.5, 9.1, 8.5$ Hz, 1H), 3.05 (ddd, $J = 17.7, 12.5, 4.0$ Hz, 1H), 2.41 (dd, $J = 5.8, 2.2$ Hz, 1H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ −117.49, −187.39. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 162.0 (C–F, ¹ $J_{CF} = 246.4$ Hz), 159.6 (C–F, ¹ $J_{CF} = 246.4$ Hz), 135.1, 127.8 (C–F, ³ $J_{CF} = 8.1$ Hz), 127.7 (C–F, ³ $J_{CF} = 8.1$ Hz), 127.2 (C–F, ³ $J_{CF} = 3.0$ Hz), 127.1 (C–F, ³ $J_{CF} = 3.0$ Hz), 117.5 (C–F, ² $J_{CF} = 23.2$ Hz), 117.3 (C–F, ² $J_{CF} = 23.2$ Hz), 116.7 (C–F, ² $J_{CF} = 22.2$ Hz), 116.5 (C–F, ² $J_{CF} = 22.2$ Hz), 90.8 (C–F, ¹ $J_{CF} = 181.8$ Hz), 89.0 (C–F, ¹ $J_{CF} = 181.8$ Hz), 68.6 (C–F, ² $J_{CF} = 20.2$ Hz), 68.4 (C–F, ² $J_{CF} = 20.2$ Hz), 26.1 (C–F, ² $J_{CF} = 24.2$ Hz), 25.9 (C–F, ² $J_{CF} = 24.2$ Hz). IR (solid) ν 3276 (br, OH), 3181, 1470, 1254, 1115, 1023 cm^{−1}. HRMS (APCI) m/z [M]⁺ calcd for C₉H₈F₂OS 202.0258, found 202.0259. SFC: Chiralpak IE, sc CO₂/MeOH 98:2, 2.0 mL/min, $P = 100$ bar, $\lambda = 215$ nm, t_R [*trans*] = 16.62 min, t_R [*trans*] = 18.39 min, t_R [*cis*-(3*S*,4*R*)] = 22.23 min, t_R [*cis*-(3*R*,4*S*)] = 23.72 min (major).

Gram-Scale Experiment. In a 30 mL round-bottom tube charged with 3-fluorochroman-4-one (**1a**, 1.0 g, 6.0 mmol, 1.0 equiv) and the catalyst (*R,R*)-**A** (7.6 mg, 12 μ mol, 0.002 equiv) set under argon was added 10 mL of acetonitrile. The mixture was stirred for 1 min before adding a (1:1) mixture of formic acid and triethylamine (5.20 mL, 16 mmol, 6.0 equiv) by syringe. The reaction mixture was stirred at 40 °C (oil bath) for 22 h. The reaction medium was cooled and quenched with 30 mL of a NaHCO₃ aqueous solution. The medium

was extracted with CH₂Cl₂ (2 \times 40 mL), and the organic layers were dried over MgSO₄, filtered, and concentrated under vacuum. The diastereoisomeric ratio was determined by ¹H NMR analysis of the crude product. The product was purified with a flash column chromatography on silica gel (petroleum ether/EtOAc 70:30), and 990 mg (98%) of (3*R*,4*R*)-3-fluorochroman-4-ol (**2a**) as a white fluffy solid was obtained. dr (*cis/trans*) 98:2, ee_{cis} > 99%. ¹H NMR (400 MHz, chloroform-*d*) δ 7.48 (dt, $J = 7.8, 1.2$ Hz, 1H), 7.26–7.20 (m, 1H), 7.00 (td, $J = 7.5, 1.2$ Hz, 1H), 6.86 (dd, $J = 8.2, 1.1$ Hz, 1H), 5.11–4.85 (m, 2H), 4.48 (ddd, $J = 12.2, 7.8, 5.6$ Hz, 1H), 4.22 (ddd, $J = 28.4, 12.2, 2.0$ Hz, 1H), 2.28 (d, $J = 6.9$ Hz, 1H). ¹⁹F{¹H} NMR (376 MHz, chloroform-*d*) δ −209.43. ¹³C{¹H} NMR (101 MHz, chloroform-*d*) δ 153.5, 130.0, 129.0, 121.8, 121.6, 116.5, 87.2 (C–F, ¹ $J_{CF} = 178.8$ Hz), 85.4 (C–F, ¹ $J_{CF} = 178.8$ Hz), 65.4 (C–F, ² $J_{CF} = 20.2$ Hz), 65.2 (C–F, ² $J_{CF} = 20.2$ Hz), 64.6 (C–F, ² $J_{CF} = 22.2$ Hz), 64.4 (C–F, ² $J_{CF} = 22.2$ Hz).

(3*R*,4*S*)-3-Fluoro-7-(4-methoxyphenyl)chroman-4-ol 3. In a round-bottom 10 mL tube charged with (3*R*,4*S*)-7-bromo-3-fluorochroman-4-ol (**2i**) (100 mg, 0.40 mmol, 1.0 equiv), (4-methoxyphenyl)boronic acid (91 mg, 0.60 mmol, 1.5 equiv), K₂CO₃ (111 mg, 0.80 mmol, 2.0 equiv), Pd(OAc)₂ (4.5 mg, 20 μ mol, 0.05 equiv), and cataCXium A (17.1 mg, 44 μ mol, 0.11 equiv) and set under argon was added 3.5 mL of DMF. The cap was screwed, and the mixture was stirred at 100 °C (oil bath) for 16 h. After this period, the reaction mixture was quenched with a saturated NaHCO₃ aqueous solution and extracted twice with CH₂Cl₂. The organic layers were dried over MgSO₄, filtered, and concentrated under vacuum. The obtained red solid was purified by flash column chromatography on silica gel (petroleum ether/EtOAc from 95:5 to 70:30), and 87 mg (79%, 0.32 mmol) of a white solid were obtained. dr (*cis/trans*) = 99:1, ee_{cis} = 99%. mp 184–186 °C. [α]_D²⁰ = −33.8 (c 1.0, acetone). ¹H NMR (400 MHz, acetone-*d*₆) δ 7.57 (d, $J = 8.8$ Hz, 2H), 7.50 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.18 (dd, $J = 7.9, 1.8$ Hz, 1H), 7.08–6.91 (m, 3H), 5.16–4.89 (m, 2H), 4.67–4.22 (m, 3H), 3.83 (s, 3H). ¹⁹F{¹H} NMR (376 MHz, acetone-*d*₆) δ −209.24. ¹³C{¹H} NMR (101 MHz, acetone-*d*₆) δ 160.5, 154.8, 142.5, 133.7, 129.9, 128.8, 122.8, 119.9, 115.2, 114.2, 88.4 (C–F, ¹ $J_{CF} = 179.8$ Hz), 86.6 (C–F, ¹ $J_{CF} = 179.8$ Hz), 66.3 (C–F, ² $J_{CF} = 22.2$ Hz), 66.0 (C–F, ² $J_{CF} = 22.2$ Hz), 65.5 (C–F, ² $J_{CF} = 20.2$ Hz), 65.3 (C–F, ² $J_{CF} = 20.2$ Hz), 55.7. IR (solid) ν 3289 (br, OH), 2937, 1470, 1250, 1182, 1110, 1024 cm^{−1}. HRMS (APCI) m/z [M + H − H₂O]⁺ calcd for C₁₆H₁₃FO₂H 257.0972, found 257.0974. SFC: Chiralpak IE, sc CO₂/MeOH 25:75, 2.0 mL/min, $P = 100$ bar, $\lambda = 215$ nm, t_R [*cis*-(3*R*,4*S*)] = 13.40 min (major), t_R [*cis*-(3*S*,4*R*)] = 20.17 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.1c01415>.

¹H, ¹⁹F, and ¹³C NMR spectra of all compounds and SFC chromatograms of the ATH products (PDF)

Accession Codes

CCDC 2086062–2086063 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to Dr. Christian Bruneau for his outstanding contribution to the field of catalysis

REFERENCES

- (1) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315.
- (2) Castelli, M.V.; Lopez, S.N. Homoisoflavonoids: Occurrence, Biosynthesis and Biological Activity. *Stud. Nat. Prod. Chem.* **2017**, *54*, 315.
- (3) Cazarolli, L. H.; Zanatta, L.; Alberton, E. H.; Figueiredo, M. S. B.; Folador, P.; Damazio, R. G.; Pizzolatti, M. G.; Silva, F. R. B. Flavonoids: Prospective Drug Candidates. *Mini-Rev. Med. Chem.* **2008**, *8*, 1429.
- (4) For selected references, see: (a) Besset, T.; Poisson, T.; Pannecoucke, X. Recent Progress in Direct Introduction of Fluorinated Groups on Alkenes and Alkynes by means of C–H Bond Functionalization. *Chem. - Eur. J.* **2014**, *20*, 16830. (b) Campbell, M. G.; Ritter, T. Modern Carbon-Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis. *Chem. Rev.* **2015**, *115*, 612. (c) Sather, A. C.; Buchwald, S. L. The Evolution of Pd⁰/Pd^{II}-Catalyzed Aromatic Fluorination. *Acc. Chem. Res.* **2016**, *49*, 2146. (d) Szpera, R.; Moseley, D. F. J.; Smith, L. B.; Sterling, A. J.; Gouverneur, V. The Fluorination of C–H Bonds: Developments and Perspectives. *Angew. Chem., Int. Ed.* **2019**, *58*, 14824. (e) Zhang, F. G.; Wang, X.-Q.; Zhou, Y.; Shi, H.-S.; Feng, Z.; Ma, J.-A.; Marek, I. Remote Fluorination and Fluoroalkyl(thiol)ation Reactions. *Chem. - Eur. J.* **2020**, *26*, 15378. (f) Ma, J.-A.; Cahard, D. Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions. *Chem. Rev.* **2004**, *104*, 6119. (g) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. Fluorine and Chirality: How to Create a Nonracemic Stereogenic Carbon-Fluorine Centre? *Chem. Soc. Rev.* **2010**, *39*, 558. (h) (a) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. Advances in Catalytic Enantioselective Fluorination, Mono-, Di-, and Trifluoromethylation, and Trifluoromethylthiolation Reactions. *Chem. Rev.* **2015**, *115*, 826. (b) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. Modern Approaches for Asymmetric Construction of Carbon-Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev.* **2018**, *118*, 3887. (c) Auria-Luna, F.; Mohammadi, S.; Divar, M.; Gimeno, M. C.; Herrera, R. P. Asymmetric Fluorination Reactions Promoted by Chiral Hydrogen Bonding-Based Organocatalysts. *Adv. Synth. Catal.* **2020**, *362*, 5275. (d) Ros, A.; Magriz, A.; Dietrich, H.; Fernández, R.; Alvarez, E.; Lassaletta, J. M. Enantioselective Synthesis of Vicinal Halohydrins via Dynamic Kinetic Resolution. *Org. Lett.* **2006**, *8*, 127. (e) Selected recent references: (a) Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. Transition Metal-Catalyzed Asymmetric Hydrogenation and Transfer Hydrogenation: Sustainable Chemistry to Access Bioactive Molecules. *Chem. Rec.* **2016**, *16*, 2754 and references cited herein.. (b) Zheng, L.-S.; Phansavath, P.; Ratovelomanana-Vidal, V. Ruthenium-Catalyzed Dynamic Kinetic Asymmetric Transfer Hydrogenation: Stereoselective Access to Syn 2-(1,2,3,4-Tetrahydro-1-Isoquinolyl)Ethanol Derivatives. *Org. Chem. Front.* **2018**, *5*, 1366. (c) Zheng, L.-S.; Féraud, C.; Phansavath, P.; Ratovelomanana-Vidal, V. Rhodium-Mediated Asymmetric Transfer Hydrogenation: A Diastereo- and Enantioselective Synthesis of Syn- α -Amido β -Hydroxy Esters. *Chem. Commun.* **2018**, *54*, 283. (d) Zheng, L.-S.; Phansavath, P.; Ratovelomanana-Vidal, V. Synthesis of Enantioenriched α,α -Dichloro- and α,α -Difluoro- β -Hydroxy Esters and Amides by Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation. *Org. Lett.* **2018**, *20*, 5107. (e) He, B.; Phansavath, P.; Ratovelomanana-Vidal, V. Rh-Mediated Asymmetric-Transfer Hydrogenation of 3-Substituted Chromones: A Route to Enantioenriched cis-3-(Hydroxymethyl)chroman-4-ol Derivatives through Dynamic Kinetic Resolution. *Org. Lett.* **2019**, *21*, 3276. (f) He, B.; Phansavath, P.; Ratovelomanana-Vidal, V. Rhodium-Catalyzed Asymmetric Transfer Hydrogenation of 4-Quinolone Derivatives. *Org. Chem. Front.* **2020**, *7*, 975. (g) Westermeyer, A.; Guillaumot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. Synthesis of Enantioenriched n-Hydroxy-y-acetal Enamides by Rhodium-catalyzed Asymmetric Transfer Hydrogenation. *Org. Lett.* **2020**, *22*, 3911. (h) Molina Betancourt, R.; Phansavath, P.; Ratovelomanana-Vidal, V. Rhodium-Catalyzed Asymmetric Transfer Hydrogenation/Dynamic Kinetic Resolution of 3-Benzylidene-Chromanones. *Org. Lett.* **2021**, *23*, 1621. (i) For selected reviews of ATH/DKR, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. Stereoselective Organic Synthesis via Dynamic Kinetic Resolution. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. (b) Pellissier, H. Recent Developments in Dynamic Kinetic Resolution. *Tetrahedron* **2011**, *67*, 3769. (c) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. Mechanistic Aspects of Transition Metal-Catalyzed Hydrogen Transfer Reactions. *Chem. Soc. Rev.* **2006**, *35*, 237. (d) Blacker, A. J. Enantioselective Transfer Hydrogenation. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 1215–1244. (e) Foubelo, F.; Nájera, C.; Yus, M. Catalytic Asymmetric Transfer Hydrogenation of Ketones: Recent Advances. *Tetrahedron: Asymmetry* **2015**, *26*, 769. (f) Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. Recent Developments in Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones and Imines through Dynamic Kinetic Resolution. *Synthesis* **2016**, *48*, 2523. (g) Matsunami, A.; Kayaki, Y. Upgrading and Expanding the Scope of Homogeneous Transfer Hydrogenation. *Tetrahedron Lett.* **2018**, *59*, 504. (h) Talavera, G.; Fariña, A. S.; Zanotti-Gerosa, A.; Nedden, H. G. Structural Diversity in Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation Reactions. In *Organometallics in Process Chemistry*; Colacot, T. J., Sivakumar, V., Eds.; Topics in Organometallic Chemistry, Vol. 65; Springer: Berlin, Germany, 2019; pp 73–114. (i) Molina Betancourt, R.; Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. Recent Progress and Applications of Transition-Metal-Catalyzed Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones and Imines through Dynamic Kinetic Resolution. *Synthesis* **2021**, *53*, 30. (j) Cotman, A. E. Escaping from Flatland: Stereoconvergent Synthesis

of Three-Dimensional Scaffolds via Ruthenium(II)-Catalyzed Noyori–Ikariya Transfer Hydrogenation. *Chem. - Eur. J.* **2021**, *27*, 39.

(12) (a) Mohar, B.; Stephan, M.; Urleb, U. Stereoselective Synthesis of Fluorine-Containing Analogues of Anti-Bacterial Sanfetrinem and LK-157. *Tetrahedron* **2010**, *66*, 4144. (b) Šterk, D.; Stephan, M.; Mohar, B. Highly Enantioselective Transfer Hydrogenation of Fluoroalkyl Ketones. *Org. Lett.* **2006**, *8*, 5935. (c) Cotman, A. E.; Cahard, D.; Mohar, B. Stereoarrayed CF₃-Substituted 1,3-Diols by Dynamic Kinetic Resolution: Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation. *Angew. Chem., Int. Ed.* **2016**, *55*, 5294. (d) Gediya, S. K.; Clarkson, G. J.; Wills, M. Asymmetric Transfer Hydrogenation: Dynamic Kinetic Resolution of α -Amino Ketones. *J. Org. Chem.* **2020**, *85*, 11309. (e) Vyas, V. K.; Clarkson, G. J.; Wills, M. Sulfone Group as a Versatile and Removable Directing Group for Asymmetric Transfer Hydrogenation of Ketones. *Angew. Chem., Int. Ed.* **2020**, *59*, 14265. (f) Caleffi, G. S.; Brum, J. D. O. C.; Costa, A. T.; Domingos, J. L. O.; Costa, P. R. R. Asymmetric Transfer Hydrogenation of Arylidene-Substituted Chromanones and Tetralones Catalyzed by Noyori–Ikariya Ru(II) Complexes: One-Pot Reduction of C–C and C–O Bonds. *J. Org. Chem.* **2021**, *86*, 4849. (g) Kießberg, A.; Lübken, T.; Metz, P. Enantioselective Total Synthesis of Natural Isoflavans: Asymmetric Transfer Hydrogenation/Deoxygenation of Isoflavanones with Dynamic Kinetic Resolution. *Org. Lett.* **2018**, *20*, 3006. (h) Qin, T.; Metz, P. Enantioselective Synthesis of Isoflavanones by Catalytic Dynamic Kinetic Resolution. *Org. Lett.* **2017**, *19*, 2981. (i) Ciesielski, P.; Metz, P. Asymmetric One-Pot Transformation of Isoflavones to Pterocarpans and Its Application in Phytoalexin Synthesis. *Nat. Commun.* **2020**, *11*, 3091. (j) Kwon, S.; Lee, S.; Heo, M.; Lee, B.; Fei, X.; Corson, T. W.; Seo, S. Y. Total Synthesis of Naturally Occurring 5,7,8-Trioxxygenated Homoisoflavonoids. *ACS Omega* **2020**, *5*, 11043.

(13) (a) Stavber, S.; Jereb, M.; Zupan, M. Direct α -Fluorination of Ketones Using N–F Reagents. *Synthesis* **2002**, 2609. (b) Zhao, Y.; Pan, Y.; Liu, H.; Yang, Y.; Jiang, Z.; Tan, C.-H. Fluorinated Aromatic Ketones as Nucleophiles in the Asymmetric Organocatalytic Formation of C–C and C–N Bonds: A Facile Route to the Construction of Fluorinated Quaternary Stereogenic Centers. *Chem. - Eur. J.* **2011**, *17*, 3571.

(14) (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. The Catalyst Precursor, Catalyst, and Intermediate in the Ru^{II}-Promoted Asymmetric Hydrogen Transfer between Alcohols and Ketones. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285. (b) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. Asymmetric Transfer Hydrogenation of α , β -Acetylenic Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

(15) (a) Echeverria, P.-G.; Féraud, C.; Phansavath, P.; Ratovelomanana-Vidal, V. Synthesis, Characterization and Use of a New Tethered Rh(III) Complex in Asymmetric Transfer Hydrogenation of Ketones. *Catal. Commun.* **2015**, *62*, 95. (b) Zheng, L.-S.; Llopis, Q.; Echeverria, P.-G.; Féraud, C.; Guillaumot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. Asymmetric Transfer Hydrogenation of (Hetero)arylketones with Tethered Rh(III)–N-(p-Tolylsulfonyl)-1,2-diphenylethylene-1,2-diamine Complexes: Scope and Limitations. *J. Org. Chem.* **2017**, *82*, 5607.

(16) Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. Oxo-Tethered Ruthenium(II) Complex as a Bifunctional Catalyst for Asymmetric Transfer Hydrogenation and H₂ Hydrogenation. *J. Am. Chem. Soc.* **2011**, *133*, 14960.

(17) (a) Yamakawa, M.; Yamada, I.; Noyori, R. CH// Attraction: the Origin of Enantioselectivity in Transfer Hydrogenation of Aromatic Carbonyl Compounds Catalyzed by Chiral b⁶-Arene-Ruthenium(II) Complexes. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818. (b) Matsuoka, A.; Sandoval, C. A.; Uchiyama, M.; Noyori, R.; Naka, H. Why *p*-Cymene? Conformational Effect in Asymmetric Hydrogenation of Aromatic Ketones with a η^6 -Arene/Ruthenium(II) Catalyst. *Chem. - Asian J.* **2015**, *10*, 112.