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Asymmetric Transfer Hydrogenation of 2,3-Disubstituted Flavanones through Dynamic Kinetic Resolution Enabled by Retro-Oxa-Michael Addition: Construction of Three Contiguous Stereogenic Centers

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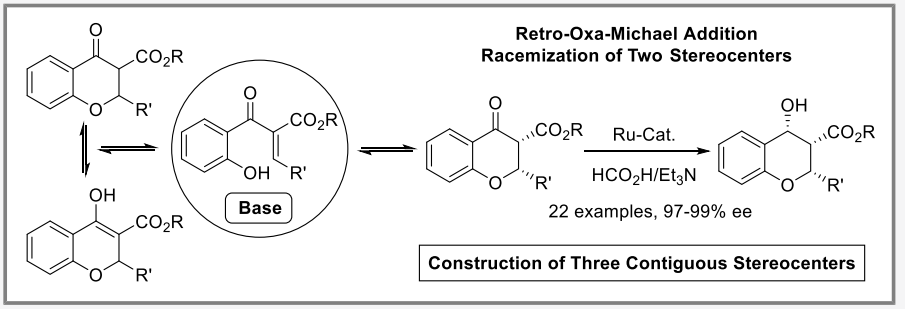

ABSTRACT: A ruthenium-catalyzed asymmetric transfer hydrogenation of 2,3-disubstituted flavanones was developed for the construction of three contiguous stereocenters under basic conditions through a combination of dynamic kinetic resolution and retro-oxa-Michael addition, giving chiral flavanols with excellent enantioselectivities and diastereoselectivities. The reaction proceeded via a base-catalyzed retro-oxa-Michael addition to racemize two stereogenic centers simultaneously in concert with a highly enantioselective ketone transfer hydrogenation step. The asymmetric transfer hydrogenation could be achieved at gram scale without loss of the activity and enantioselectivity.

The development of straightforward and effective access for the preparation of enantiomerically enriched compounds with multiple stereocenters from relatively simple starting materials is an ideal goal for chemists. Kinetic resolution has become one of the important solutions to chiral compounds,[1] including classical kinetic resolution and dynamic kinetic resolution (DKR). Since it results in 100% of the maximum theoretical yield, dynamic kinetic resolution has attracted continuous interest, and has become an efficient class of reactions for the synthesis of complex chiral molecules, allowing multiple stereocenters to be set in a single transformation from readily available racemic starting materials.[2] Well-known examples included DKR reductions of α-substituted ketones,[3] which proceeds through classical enolization-induced substrate racemization. A few works on DKR reductions of β-substituted ketones for construction of two discrete stereocenters were reported by MacMillan,[4] Vidal,[5] Peng,[6] Liu,[7] Sherer[8] and other groups.[9] However, DKR reduction of α,β-disubstituted ketones is rare, which is a challenge in organic synthesis and requires rapid racemization of two stereogenic centers. An example was reported by Sherer's group, who developed a Ru-catalyzed transfer hydrogenation of tricyclic chromanones to afford the chiral chromanols with three contiguous stereocenters.[8] Therefore, the development of a concise and efficient asymmetric hydrogenation of α,β-disubstituted ketones involving DKR and rapid racemization of two stereogenic centers represents a compelling research objective.

Chiral flavanol derivatives constitute a large class of important molecules and feature a variety of useful bioactivities (Figure 1) such as antiviral, antibacterial, and antifungal effects.[10] Although substantial progresses have been gained on the synthesis of chiral flavanols,[11] some of them are limited in substrate scope and catalyst efficiency. The construction of functionalized flavanols with three chiral centers is still a challenge in synthetic organic chemistry.

Asymmetric (transfer) hydrogenation of multiple substituted ketones has been regarded as a promising method to synthesize functional chiral alcohol derivatives using transition-metal catalysts.[12,13] Recently, our group observed that

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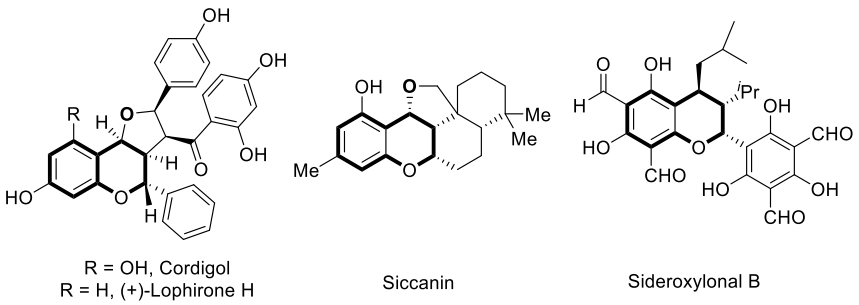
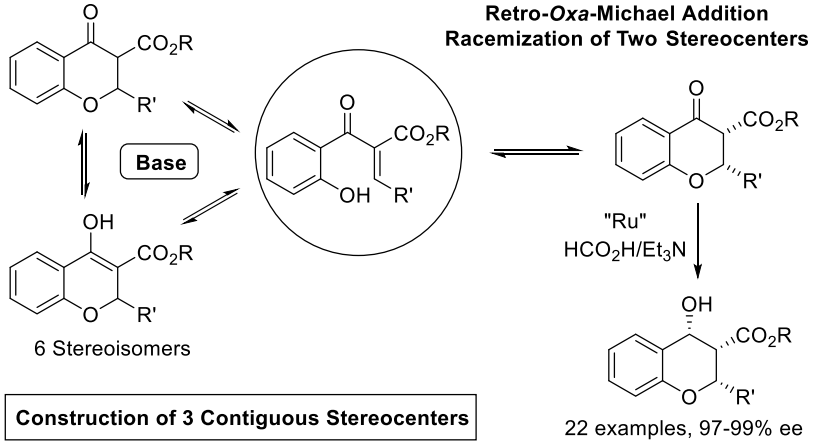


Figure 1. Some bioactive natural products containing a flavanol motif.

Scheme 1. Ru-Catalyzed ATH of 2,3-Disubstituted Flavanones



2,3-disubstituted flavanones are easy to proceed retro-oxa-Michael addition[14] under basic conditions, leading to racemization of two stereocenters simultaneously. Then, a palladium-catalyzed asymmetric allylic alkylation with this strategy was achieved, constructing chiral flavanone derivatives with two contiguous stereocenters (including a quaternary stereogenic center).[15] Encouraged by this result, we envisioned whether this strategy could be utilized in the asymmetric reduction of flavanoids with a basic catalyst system, which would enable enantioselective synthesis of flavanols with three contiguous stereogenic centers (Scheme 1). Herein, we report a Ru-catalyzed transfer hydrogenation of readily available 2,3-disubstituted flavanones, delivering the stereoarrayed flavanols. This approach features atom economy, broad substrate scope, high activity, enantio- and diastereoselectivity.

To investigate the proposed hypothesis, we moved toward the examination of transition metal-catalyzed transfer hydrogenation with **1a** as a model substrate. Some experimental results of condition optimization were summarized in Table 1. In the beginning, the reaction was carried out in solvent ethyl acetate with a ruthenium complex originally developed by Noyori's group.[16] The reductive product could be obtained in 83% yield, 94% ee, and 4:1 diastereoselectivity (Table 1, entry 1). Further evaluation of other protic and aprotic solvents indicated that polar aprotic solvent *N*,*N*-dimethylformamide was optimal with regard to enantio- and diastereoselectivity and activity (entries 2−6). Next, we started to investigate the ruthenium catalyst property. When replacing Ru catalyst (*R*,*R*)-**3a** with (*R*,*R*)-**3b**, the desirable hydrogenation product could be obtained, albeit with low diastereoselectivity (entry 7). Excellent activity and enantioselectivity were obtained with catalyst (*R*,*R*)-**3c** (entry 8). Unfortunately, 3:1 diastereoselectivity was observed when (*R*,*R*)-**3d** was used as transfer hydrogenation catalyst (entry 9). Then, the catalyst loading and the amount of HCO_2H/Et_3N were screened, and found that 2 mol % Ru-catalyst and five equivalent amounts of HCO_2H/Et_3N were optimal. Thus, the optimal reaction condition was identified: 2,3-disubstituted flavanones **1** (0.2 mmol), Ru-catalyst **3a** (2.0 mol %), HCO_2H/Et_3N (0.08 mL, 5.0 equiv), DMF and 40 °C.

With optimal conditions in hand, the substrate scope of flavanones **1** was explored (Table 2). As expected, most flavanones **1** performed well under the standard conditions. The different esters were first examined in this reaction; good yields and excellent enantioselectivities were obtained (**2a**−**2f**). The best result was obtained for the ester with methyl group (**2b**). Next, the steric properties of the substituents on aryl group of R′ were explored when R was cyclohexyl (**2g**−**2i**), and had rare influence on the reaction except the substrate (**2i**); when methyl was introduced into the *ortho*-position, the significantly decreased yields were observed due to steric hindrance. Either electron-donating or electron-withdrawing substituents on the aryl group could also achieve excellent results (**2j**−**2l**, **2n**−**2o**). However, **2m** which possessed a 4-fluorophenyl was obtained in excellent yield but a little lower enantioselectivity. As for the alkyl-substituted substrates chromanones **2p**−**2q**, high enantioselectivity could be also obtained, albeit with lightly decreased activity. Notably, the substituents on the aromatic ring containing methyl, methoxy, or bromo had little influence on the enantioselectivity. However, moderate yield of **2v** was obtained, which may be due to the large steric hindrance of the methoxy at the *ortho*-position. Gratifyingly, the diastereoselectivity of all substrates could be excellently controlled (dr >20:1). The absolute

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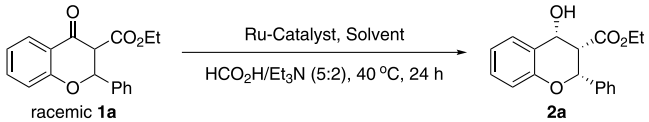
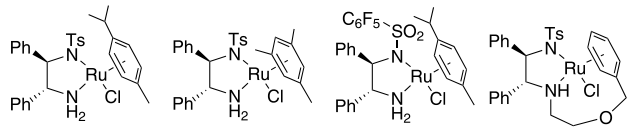
Table 1. Optimization of Ru-Catalyzed Asymmetric Transfer Hydrogenation





entry[a]	solvent	Ru-cat.	conv. (%)[b]	ee (%)[c]	dr (%)[d,e]
1	EA	(*R*,*R*)-**3a**	83	93.7	4:1
2	^{i}PrOH	(*R*,*R*)-**3a**	>95	98.6	>20:1
3	DCM	(*R*,*R*)-**3a**	>95	98.4	9:1
4	Toluene	(*R*,*R*)-**3a**	71	87.8	4:1
5	THF	(*R*,*R*)-**3a**	80	96.0	5:1
6	DMF	(*R*,*R*)-**3a**	>95	99.5	>20:1
7	DMF	(*R*,*R*)-**3b**	>95	98.7	5:1
8	DMF	(*R*,*R*)-**3c**	95	99.2	>20:1
9	DMF	(*R*,*R*)-**3d**	78	98.8	3:1
10[f]	DMF	(*R*,*R*)-**3a**	>95	98.8	>20:1
11[g]	DMF	(*R*,*R*)-**3a**	88	99.6	>20:1
12[f,h]	DMF	(*R*,*R*)-**3a**	>95	99.4	>20:1
13[f,i]	DMF	(*R*,*R*)-**3a**	>95(96)[j]	99.0	>20:1

[a]**1a** (0.2 mmol), solvent (2.0 mL), HCO_2H/Et_3N (0.5 mL, 30.0 equiv), Ru-cat. (5.0 mol %), 40 °C, 24 h. [b]Measured by analysis of ^{1}H NMR. [c]Determined by HPLC. [d]Determined by analysis of ^{1}H NMR. [e]The structure of the product was assigned as (*cis*, *cis*) and (*trans*, *trans*); (*cis*, *trans*) and (*cis*, *trans*) were not found. [f]Ru-cat. (2.0 mol %). [g]Ru-cat. (1.0 mol %). [h]HCO_2H/Et_3N (0.25 mL, 15.0 equiv). [i]HCO_2H/Et_3N (0.08 mL, 5.0 equiv). [j]Isolated yield. EA = ethyl acetate, DCM = dichloromethane, ^{i}PrOH = isopropanol, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

configuration of **2a** was assigned as (2*R*,3*S*,4*R*) by X-ray diffraction analysis, and other products were assigned by analogy (for details, please see the Supporting Information).

To showcase the utility of this methodology, some transformations were conducted as shown in Scheme 2. First, when substrate **1a** was conducted at 3.5 mmol scale, 99% ee and 95% yield were obtained without any loss of activity and enantioselectivity. Considering that carbonyl is a versatile functional group, transformation of chiral product **2a** was carried out with $LiAlH_4$ as the reductant to afford the chiral dihydroxy **4** with 80% yield and 98% ee. Esterification with acetic anhydride delivered the diester **5** in 93% yield and 99% ee.

To further verify the above reaction process, two control experiments were conducted; asymmetric transfer hydrogenation of **1a** was performed by using (*R*,*R*)-**3a** or (*S*,*S*)-**3a** under the optimal conditions, respectively. The products with opposite configuration were obtained with the same ee values (Scheme 3).

On the basis of the above experimental results and putative mechanism on ruthenium-catalyzed asymmetric hydrogenation,[16] a possible reaction pathway was proposed (Scheme 4). First, a rapid racemization of **1a** was performed to obtain (2*R*,3*R*)-**1a** and three other isomers under the basic conditions through a retro-oxa-Michael addition process. The asymmetric transfer hydrogenation happened with isomer (2*R*,3*R*)-**1a** suitably, which avoided the disfavored steric interaction between the phenyl ring of the ligand and the substrate. As a result, chiral product (2*R*,3*S*,4*R*)-**2a** was obtained preferentially.

In conclusion, we have successfully developed an asymmetric transfer hydrogenation of 2,3-disubstituted flavanones through dynamic kinetic resolution enabled by retro-oxa-Michael addition for the construction of three contiguous stereogenic centers. A broad range of highly enantiomerically enriched flavanols could be conveniently prepared with up to >99% ee. Efforts to expand the application of this strategy to other substrates are underway in our laboratory.

EXPERIMENTAL SECTION

All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques, unless otherwise noted. Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. ^{1}H NMR, ^{13}C{^{1}H} NMR, and ^{19}F{^{1}H} NMR spectra were recorded at room temperature in $CDCl_3$ or CD_2Cl_2 on 400 MHz instrument with tetramethylsilane as internal standard. The following abbreviations were used to symbolize the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, brs = broad singlet. Enantiomeric excess was determined by HPLC analysis, using chiral column described below in detail. Optical rotations were measured by polarimeter. Flash column chromatography was performed on silica gel (200−300 mesh). All reactions were monitored by TLC analysis. High-resolution mass spectrometry (HRMS(ESI-TOF) *m*/*z*) was measured on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry. The heat source for all heating reactions was the oil bath.

Procedures for Synthesis of 2,3-Disubstituted Flavanones 1. *Method A.* 2,3-Disubstituted flavanones **1a**−**1t** could be conveniently prepared from the readily available 2-substituted 4-oxo-4*H*-chromene-3-carboxylic acid esters **S1** through the biomimetic reduction. Intermediates **S1** could be prepared from readily available 2-fluoroaryl formyl chloride and *beta*-ketoester according to the known literature procedure with minor modification.[17] Among them, **S1a**,**b**,[18a] **S1c**,[18b] **S1d**−**f**,[18c] **S1g**−**i**,[18b] **S1j**,[18d] **S1k**,[18c] **S1m**,[18c] **S1n**,**o**,[18e] and **S1p**−**t**[18b] are known compounds.

Under nitrogen, *beta*-ketoester (10.0 mmol, 1.0 equiv, 0.5 M) was dissolved in dry toluene (20 mL). Sodium hydride (11.0 mmol, 1.1 equiv) was added and the mixture was stirred at room temperature for 30 min. Then, the solution of 2-fluoroaryl formyl chloride (10.0 mmol, 1.0 equiv, 0.5 M) in dry toluene (20 mL) was added dropwise to the stirred mixture. After that, the reaction was stirred under reflux overnight. The mixture was cooled to ambient temperature and quenched with water (20 mL). Then, the mixture was extracted with ethyl acetate (40 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under the reduced pressure. The residue was purified by flash column chromatography on silica gel using hexanes/ethyl acetate as eluent. The solid products **S1a**−**1t** could be obtained by recrystallization from dichloromethane/hexanes.

*Methyl 2-(3-methoxyphenyl)-4-oxo-4H-chromene-3-carboxylate (**S1l**).* 1.50 g, 54% yield, pale yellow oil, new compound, R_f = 0.15 (hexanes/ethyl acetate 5/1), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.66−7.64 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.40−7.34 (m, 2H), 7.28−7.22 (m, 2H), 7.06−7.03 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.9, 165.6, 162.7, 159.8, 155.7, 134.4, 133.0, 130.0, 126.0, 125.7, 123.0, 120.3, 118.2, 118.1, 117.5, 113.2, 55.5, 52.8. HRMS (ESI-TOF) *m*/*z* calculated for $C_{18}H_{15}O_5$ $[M + H]^+$ 311.0914, found 311.0913.

Flavanones **1a**−**1t** could be obtained by hydrogenation of intermediates **S1a**−**1t** according to known literature methods with minor modifications.[18b] Among them, compounds **1a**,[19a] **1b**,[18d] **1j**−**k**,[18d] **1m**,[18d] and **1n**,**o**[19b] are the known compounds.

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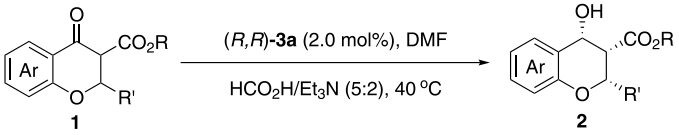
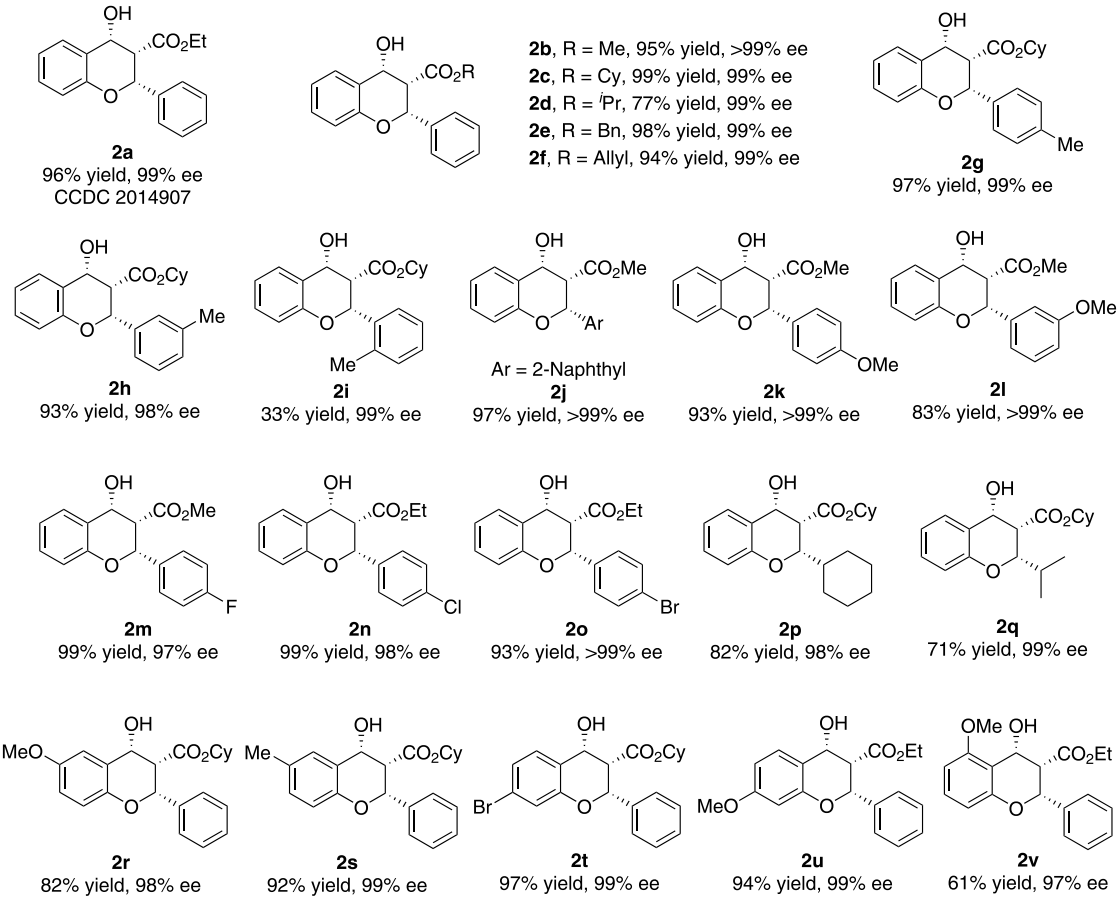
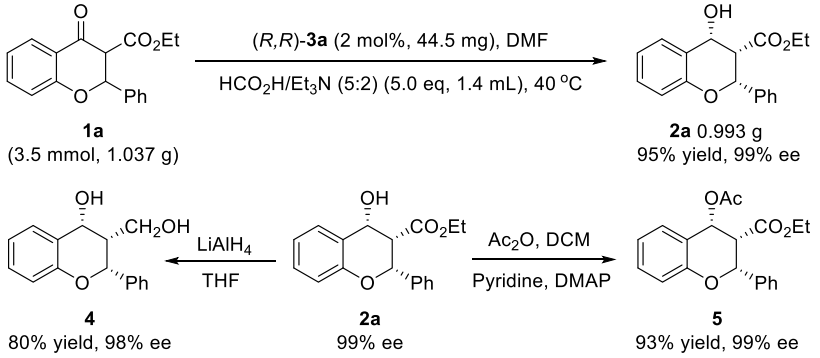
Table 2. Substrate Scope for the Synthesis of Chiral 2,3-Disubstituted Flavanols





Scheme 2. Scale-up Experiment and Transformations of Chiral Product 2a



A mixture of $[Ru(p\text{-cymene})I_2]_2$ (9.8 mg, 0.01 mmol, 0.5 mol %), samarium trifluoromethanesulfonate (239.0 mg, 0.4 mmol, 20 mol %), phenanthridine (PD) (35.9 mg, 0.2 mmol, 10 mol %), and **S1** (2.0 mmol, 0.17 M) in ethyl acetate (12 mL) was stirred at room temperature for 5 min in glovebox and then the mixture was transferred to an autoclave. The hydrogenation was performed at 50 °C under hydrogen gas (800 psi) for 24 h. The reaction mixture was concentrated under the reduced pressure to remove the volatiles, and the residue was purified by column chromatography on silica gel using hexanes and ethyl acetate as eluent to give the desirable substrate 2,3-disubstituted flavanones **1a**−**1t**.

Method B. Flavanones **1u** and **1v** could be prepared from the readily available 2′-hydroxyacetophenone derivatives according to the reported procedure.[19a] To a solution of 1-(2-hydroxy-methoxyphenyl)ethan-1-one (1.662 g, 10 mmol, 1.0 equiv, 0.25 M) in THF (40 mL) was added the diethyl carbonate (2.362 g, 20 mmol, 2.0 equiv). After the reaction mixture was stirred at 0 °C for about 10 min, sodium hydride (1.200 g, 30 mmol, 3.0 equiv, 60% in oil) was

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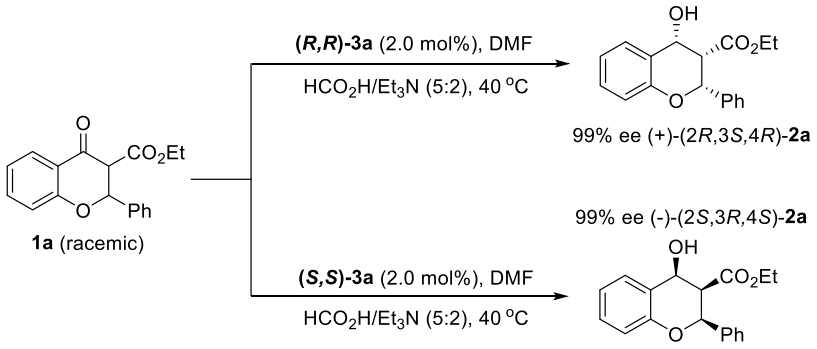
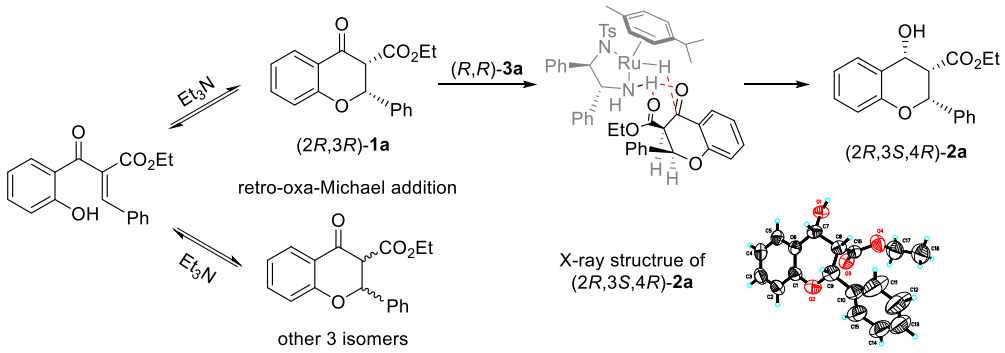
Scheme 3. Control Experiments



Scheme 4. Proposed Possible Reaction Pathway



added at the same temperature. Then, the mixture was heated to reflux until TLC indicated the full consumption of the ketone. The solvent was removed in a vacuum and the residue was mixed with water (50 mL), acidified with aqueous HCl (3 M) to pH 3−4, and extracted with ethyl acetate (30 mL × 3). The combined organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexanes and ethyl acetate as eluent to give the intermediate which was used in the next step directly.

The intermediate (7.17 mmol, 1.0 equiv, 0.24 M) was dissolved in ethanol (30 mL) followed by addition of benzaldehyde (0.761 g, 7.17 mmol, 1.0 equiv). After that, piperidine (122 mg, 1.43 mmol, 20 mmol %) was added to the above ethanol solution. The resulting mixture was stirred at ambient temperature for about 12 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica gel using hexanes and ethyl acetate as eluent to give the desired 2,3-disubstituted flavanones **1u** and **1v**.

Notably, due to the rapid interconversion between keto−enol and *cis-trans* isomerisms for 2,3-disubstituted flavanones **1**, it is difficult to obtain a relatively clean ^{1}H and ^{13}C{^{1}H} NMR spectra. Fortunately, 2,3-disubstituted flavanones **1** could be directly used in the asymmetric transfer hydrogenation without any unexpected side effect.

General Procedure for Ru-Catalyzed ATH of 2,3-Disubstituted Flavanones. Under the nitrogen atmosphere, a mixture of 2,3-disubstituted flavanones **1** (0.2 mmol, 1.0 equiv) and RuCl[(*R*,*R*)-Tsdpen](*p*-cymene) catalyst **3a** (2.6 mg, 0.004 mmol, 2 mol %) in an azeotrope of formic acid, triethylamine (5:2, 80 μL, 1.0 mmol, 5.0 equiv), and *N*,*N*-dimethylformamide (DMF, 2.0 mL) was stirred at 40 °C for 17−60 h. After being cooled to ambient temperature, ethyl acetate (20 mL) was added, and then the mixture was washed with water (3 × 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under the reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/ethyl acetate as eluent to afford the desired reductive products **2**. The optical purity was determined by chiral HPLC analysis. The racemates could be synthesized through the above transfer hydrogenation procedure with the racemic catalyst RuCl[(±)-Tsdpen](*p*-cymene).

*(+)-(2R,3S,4R)-Ethyl 4-hydroxy-2-phenylchromane-3-carboxylate (**2a**).* Reaction time: 24 h, 57 mg, 96% yield, white solid, mp = 167−168 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 3/1), 99% ee, $[\alpha]^{20}_{D}$ = +28.82 (*c* 0.68, $CHCl_3$), ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.58 (d, *J* = 7.7 Hz, 1H), 7.47−7.34 (m, 5H), 7.27−7.21 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 5.42 (d, *J* = 2.4 Hz, 1H), 5.26 (dd, *J* = 10.5, 6.3 Hz, 1H), 3.86−3.91 (m, 2H), 3.49 (dd, *J* = 6.3, 2.5 Hz, 1H), 2.84 (dd, *J* = 10.5, 5.4 Hz, 1H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2) δ 169.5, 154.3, 138.6, 128.8, 128.2, 127.8, 127.1, 125.6, 125.1, 121.5, 116.0, 77.2, 66.6, 60.5, 50.8, 13.5. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 23.6 and 26.3 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{18}H_{18}NaO_4$ $[M + Na]^+$ 321.1097, found 321.1095.

*(+)-Methyl 4-hydroxy-2-phenylchromane-3-carboxylate (**2b**).* Reaction time: 24 h, 54 mg, 95% yield, white solid, mp = 210−211 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 3/1), > 99% ee, $[\alpha]^{20}_{D}$ = +57.45 (*c* 0.59, $CHCl_3$), ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.42−7.34 (m, 5H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 5.40 (d, *J* = 2.4 Hz, 1H), 5.27 (dd, *J* = 9.6, 6.5 Hz, 1H), 3.50 (dd, *J* = 6.3, 2.5 Hz, 1H), 3.42 (s, 3H), 2.78 (d, *J* = 10.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2) δ 170.3, 154.7, 138.9, 129.3, 128.7, 128.4, 127.5, 125.9, 125.3, 121.9, 116.4, 77.6, 66.9, 51.7, 51.4. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 27.3 and 31.1 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{17}H_{20}NO_4$ $[M + NH_4]^+$ 302.1387, found 302.1387.

*(+)-Cyclohexyl 4-hydroxy-2-phenylchromane-3-carboxylate (**2c**).* Reaction time: 24 h, 72 mg, 99% yield, white solid, mp = 202−203 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 5/1), 99% ee, $[\alpha]^{20}_{D}$ = +38.52 (*c* 0.85, $CHCl_3$), ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.61 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.52−7.50 (m, 2H), 7.46−7.42 (m, 2H), 7.39−7.37 (m, 1H), 7.29−7.25 (m, 1H), 7.07 (td, *J* = 7.5, 1.2 Hz, 1H), 6.97 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.46 (d, *J* = 2.5 Hz, 1H), 5.31 (d, *J* = 6.3 Hz, 1H), 4.65 (tt, *J* = 8.1, 3.8 Hz, 1H), 3.55 (dd,

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J = 6.3, 2.5 Hz, 1H), 2.89 (brs, 1H), 1.65−1.61 (m, 1H), 1.53−1.47 (m, 1H), 1.45−1.38 (m, 2H), 1.31−1.24 (m, 3H), 1.12−1.19 (m, 2H), 0.93−1.03 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2) δ 169.2, 154.7, 138.9, 129.1, 128.6, 128.1, 127.4, 126.0, 125.7, 121.8, 116.4, 77.4, 73.5, 67.2, 51.2, 31.6, 31.3, 25.6, 23.5, 23.4. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 16.4 and 21.0 min (major). HRMS (ESI-TOF) m/z calculated for $C_{22}H_{24}NaO_4$ $[M + Na]^+$ 375.1567, found 375.1534.

*(+)-Isopropyl 4-hydroxy-2-phenylchromane-3-carboxylate (**2d**).* Reaction time: 24 h, 48 mg, 77% yield, white solid, mp = 155−156 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate 5/1), 99% ee, $[\alpha]^{20}_D$ = +35.41 (c 0.96, $CHCl_3$), ^1H NMR (400 MHz, CD_2Cl_2) δ 7.59 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.3 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.27−7.22 (m, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 5.42 (d, J = 2.3 Hz, 1H), 5.26 (dd, J = 10.2, 6.3 Hz, 1H), 4.84−4.74 (m, 1H), 3.48 (dd, J = 6.3, 2.5 Hz, 1H), 2.94 (d, J = 10.4 Hz, 1H), 1.01 (d, J = 6.3 Hz, 3H), 0.80 (d, J = 6.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2) δ 169.4, 154.7, 138.9, 129.1, 128.5, 128.1, 127.4, 126.0, 125.6, 121.8, 116.3, 77.4, 68.7, 67.1, 51.1, 21.7, 21.4. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 16.0 and 19.2 min (major). HRMS (ESI-TOF) m/z calculated for $C_{19}H_{20}NaO_4$ $[M + Na]^+$ 335.1254, found 335.1257.

*(+)-Benzyl 4-hydroxy-2-phenylchromane-3-carboxylate (**2e**).* Reaction time: 24 h, 71 mg, 98% yield, white solid, mp = 179−180 °C, new compound, R_f = 0.25 (hexanes/ethyl acetate 5/1), 99% ee, $[\alpha]^{20}_D$ = +21.43 (c 0.84, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.7 Hz, 1H), 7.41−7.38 (m, 2H), 7.35−7.29 (m, 3H), 7.26−7.18 (m, 4H), 7.06−7.02 (m, 1H), 6.95 (dd, J = 8.2, 1.0 Hz, 1H), 6.85 (dd, J = 7.8, 1.5 Hz, 2H), 5.40 (d, J = 2.4 Hz, 1H), 5.29 (dd, J = 10.3, 6.4 Hz, 1H), 4.89 (q, J = 12.5 Hz, 2H), 3.59 (dd, J = 6.3, 2.5 Hz, 1H), 2.80 (d, J = 10.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 154.3, 138.3, 135.1, 129.2, 128.5, 128.4, 128.2, 128.04, 127.98, 127.2, 125.6, 121.9, 116.5, 77.2, 66.9, 66.5, 51.1. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 85/15, flow = 0.7 mL/min, retention time 20.9 and 26.1 min (major). HRMS (ESI-TOF) m/z calculated for $C_{23}H_{24}NO_4$ $[M + NH_4]^+$ 378.1700, found 378.1669.

*(+)-Allyl 4-hydroxy-2-phenylchromane-3-carboxylate (**2f**).* Reaction time: 24 h, 29 mg (0.1 mmol scale), 94% yield, white solid, mp = 148−149 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate 5/1), 99% ee, $[\alpha]^{20}_D$ = +35.61 (c 0.82, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.7 Hz, 1H), 7.46 (dd, J = 4.5, 4.0 Hz, 2H), 7.42−7.38 (m, 2H), 7.35−7.33 (m, 1H), 7.24−7.22 (m, 1H), 7.05 (td, J = 7.5, 1.1 Hz, 1H), 6.96 (dd, J = 8.2, 1.0 Hz, 1H), 5.57−5.48 (m, 1H), 5.42 (d, J = 2.4 Hz, 1H), 5.30 (s, 1H), 5.05−5.00 (m, 1H), 4.96−4.91 (m, 1H), 4.38−4.35 (m, 2H), 3.57 (dd, J = 6.3, 2.5 Hz, 1H), 2.84 (brs, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 154.2, 138.3, 131.2, 129.1, 128.4, 128.0, 127.1, 125.5, 124.7, 121.7, 118.2, 116.3, 77.1, 66.7, 65.2, 51.0. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 27.0 and 28.8 min (major). HRMS (ESI-TOF) m/z calculated for $C_{19}H_{22}NO_4$ $[M + NH_4]^+$ 328.1543, found 328.1543.

*(+)-Cyclohexyl 4-hydroxy-2-(p-tolyl)chromane-3-carboxylate (**2g**).* Reaction time: 24 h, 71 mg, 97% yield, white solid, mp = 180−181 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 5/1), 99% ee, $[\alpha]^{20}_D$ = +41.15 (c 0.78, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.57 (m, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.24−7.18 (m, 3H), 7.02 (td, J = 7.5, 1.1 Hz, 1H), 6.94 (dd, J = 8.2, 1.0 Hz, 1H), 5.38 (d, J = 2.1 Hz, 1H), 5.26 (s, 1H), 4.69- 4.63 (m, 1H), 3.50 (dd, J = 6.2, 2.5 Hz, 1H), 2.88 (brs, 1H), 2.36 (s, 3H), 1.62−1.57 (m, 1H), 1.50−1.38 (m, 2H), 1.36−1.32 (m, 1H), 1.30−1.20 (m, 3H), 1.18−1.09 (m, 2H), 1.05−0.98 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.2, 154.4, 137.5, 135.4, 129.0, 127.1, 125.6, 125.1, 121.9, 121.6, 118.3, 116.3, 77.1, 73.2, 67.0, 50.9, 31.3, 31.0, 25.3, 23.1, 23.0, 21.3. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 14.8 and 18.4 min (major). HRMS (ESI-TOF) m/z calculated for $C_{23}H_{26}NaO_4$ $[M + Na]^+$ 389.1723, found 389.1724.

*(+)-Cyclohexyl 4-hydroxy-2-(m-tolyl)chromane-3-carboxylate (**2h**).* Reaction time: 36 h, 68 mg, 93% yield, white solid, mp = 119−120 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 5/1), 98% ee, $[\alpha]^{20}_D$ = +40.51 (c 0.98, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.7 Hz, 1H), 7.30−7.26 (m, 2H), 7.26−7.21 (m, 2H), 7.13 (d, J = 7.1 Hz, 1H), 7.03 (td, J = 7.5, 1.1 Hz, 1H), 6.96 (dd, J = 8.2, 1.0 Hz, 1H), 5.37 (d, J = 2.2 Hz, 1H), 5.27 (dd, J = 9.7, 6.4 Hz, 1H), 4.68−4.62 (m, 1H), 3.51 (dd, J = 6.3, 2.4 Hz, 1H), 2.94 (d, J = 10.6 Hz, 1H), 2.39 (s, 3H), 1.60 (dd, J = 13.5, 7.0 Hz, 1H), 1.48−1.33 (m, 3H), 1.27−1.19 (m, 3H), 1.17−1.08 (m, 2H), 1.01−0.92 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.1, 154.3, 138.3, 137.8, 128.9, 128.5, 128.2, 127.0, 126.2, 125.1, 122.7, 121.5, 116.2, 77.1, 73.2, 67.0, 50.8, 31.2, 31.0, 25.2, 23.1, 23.0, 21.6. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 14.8 and 19.9 min (major). HRMS (ESI-TOF) m/z calculated for $C_{23}H_{30}NO_4$ $[M + NH_4]^+$ 384.2169, found 384.2162.

*(+)-Cyclohexyl 4-hydroxy-2-(o-tolyl)chromane-3-carboxylate (**2i**).* Reaction time: 60 h, 24 mg, 33% yield, colorless viscous oil, new compound, R_f = 0.50 (hexanes/ethyl acetate 5/1), 99% ee, $[\alpha]^{20}_D$ = +43.86 (c 0.44, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 5.0, 3.4 Hz, 2H), 7.25−7.17 (m, 4H), 7.03 (td, J = 7.6, 1.0 Hz, 1H), 6.92 (dd, J = 8.2, 0.8 Hz, 1H), 5.49 (d, J = 2.0 Hz, 1H), 5.27 (t, J = 7.0 Hz, 1H), 4.64−4.62 (m, 1H), 3.45 (dd, J = 6.4, 2.2 Hz, 1H), 2.79 (d, J = 10.4 Hz, 1H), 2.35 (s, 3H), 1.48−1.44 (m, 2H), 1.37−1.28 (m, 2H), 1.27−1.10 (m, 5H), 0.97−0.94 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.9, 154.6, 136.3, 133.3, 130.3, 128.8, 127.8, 126.9, 126.1, 126.0, 125.1, 121.6, 116.2, 75.0, 73.4, 67.0, 48.8, 31.3, 31.0, 25.2, 23.3, 23.2, 19.0. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 14.2 and 18.2 min (major). HRMS (ESI-TOF) m/z calculated for $C_{23}H_{30}NO_4$ $[M + NH_4]^+$ 384.2169, found 384.2140.

*(+)-Methyl 4-hydroxy-2-(naphthalen-2-yl)chromane-3-carboxylate (**2j**).* Reaction time: 24 h, 65 mg, 97% yield, white solid, mp = 199−202 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 5/1), > 99% ee, $[\alpha]^{20}_D$ = +95.49 (c 1.22, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.90−7.87 (m, 3H), 7.62 (d, J = 7.7 Hz, 1H), 7.53−7.49 (m, 3H), 7.33−7.29 (m, 1H), 7.09−7.01 (m, 2H), 5.55 (d, J = 2.1 Hz, 1H), 5.33 (t, J = 7.2 Hz, 1H), 3.64 (dd, J = 6.3, 2.5 Hz, 1H), 3.38 (s, 3H), 2.89 (d, J = 10.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.1, 154.3, 135.8, 133.2, 133.1, 129.1, 128.12, 128.05, 127.8, 127.2, 126.3, 126.2, 124.7, 124.5, 123.4, 121.8, 116.4, 77.4, 66.8, 51.5, 50.9. HPLC: Chiralpak AS-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 92/8, flow = 0.7 mL/min, retention time 31.6 min (major) and 34.2 min. HRMS (ESI-TOF) m/z calculated for $C_{21}H_{22}NO_4$ $[M + NH_4]^+$ 352.1543, found 352.1543.

*(+)-Methyl 4-hydroxy-2-(4-methoxyphenyl)chromane-3-carboxylate (**2k**).* Reaction time: 48 h, 56 mg, 93% yield, white solid, mp = 222−223 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate 5/1), > 99% ee, $[\alpha]^{20}_D$ = +75.42 (c 0.70, $CHCl_3$), ^1H NMR (400 MHz, CD_2Cl_2) δ 7.55 (d, J = 7.7 Hz, 1H), 7.34−7.31 (m, 2H), 7.23−7.21 (m, 1H), 7.03 (td, J = 7.5, 1.1 Hz, 1H), 6.94−6.89 (m, 3H), 5.35 (d, J = 2.5 Hz, 1H), 5.25 (dd, J = 9.9, 6.4 Hz, 1H), 3.82 (s, 3H), 3.48−3.41 (m, 4H), 2.69 (d, J = 10.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2) δ 169.9, 159.4, 154.5, 130.5, 128.8, 127.1, 126.8, 124.8, 121.4, 116.0, 113.6, 77.0, 66.5, 55.2, 51.3, 51.1. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 85/15, flow = 0.7 mL/min, retention time 21.0 and 25.6 min (major). HRMS (ESI-TOF) m/z calculated for $C_{18}H_{18}NaO_5$ $[M + Na]^+$ 337.1046, found 337.1039.

*(+)-Methyl 4-hydroxy-2-(3-methoxyphenyl)chromane-3-carboxylate (**2l**).* Reaction time: 48 h, 50 mg, 83% yield, white solid, mp = 118−120 °C, new compound, R_f = 0.2 (hexanes/ethyl acetate 5/1), > 99% ee, $[\alpha]^{20}_D$ = +55.86 (c 1.04, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.7 Hz, 1H), 7.33−7.29 (m, 1H), 7.23 (td, J = 7.4, 3.8 Hz, 1H), 7.04 (td, J = 7.6, 1.1 Hz, 1H), 7.01−6.94 (m, 3H), 6.90−6.88 (m, 1H), 5.37 (d, J = 2.3 Hz, 1H), 5.27 (dd, J = 10.9, 6.6 Hz, 1H), 3.83 (s, 3H), 3.52 (dd, J = 6.3, 2.5 Hz, 1H), 3.46 (s, 3H), 2.79 (d, J = 10.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.1, 159.7, 154.2, 140.0, 129.4, 129.1, 127.2, 124.6, 121.8, 117.8,

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116.4, 113.5, 111.2, 77.1, 66.7, 55.3, 51.5, 50.9. HPLC: Chiralpak AS-H column, 220 nm, 30 °C, *n*-Hexane /*i*-PrOH = 85/15, flow = 0.7 mL/min, retention time 17.6 min (major) and 27.9 min. HRMS (ESI-TOF) *m*/*z* calculated for $C_{18}H_{22}NO_5$ $[M + NH_4]^+$ 332.1492, found 332.1491.

*(+)-Methyl 2-(4-fluorophenyl)-4-hydroxychromane-3-carboxylate (**2m**).* Reaction time: 17 h, 61 mg, 99% yield, white solid, mp = 235−237 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 5/1), 97% ee, $[\alpha]^{20}_D$ = +47.10 (*c* 1.14, $CHCl_3$), ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.42 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.25 (dd, *J* = 11.3, 4.1 Hz, 1H), 7.11 (t, *J* = 8.8 Hz, 2H), 7.06 (dd, *J* = 10.9, 4.0 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 5.41 (d, *J* = 1.9 Hz, 1H), 5.28 (dd, *J* = 10.1, 6.4 Hz, 1H), 3.49 (dd, *J* = 6.3, 2.5 Hz, 1H), 3.44 (s, 3H), 2.75 (d, *J* = 10.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2) δ 169.8, 162.4 (d, $^1J_{F-C}$ = 245.2 Hz), 154.1, 134.4, 128.9, 127.3 (d, $^3J_{F-C}$ = 8.1 Hz), 127.1, 124.8, 121.6, 116.0, 115.1 (d, $^2J_{F-C}$ = 22.0 Hz), 76.6, 66.4, 51.4, 50.9. $^{19}F\{^1H\}$ NMR (376 MHz, CD_2Cl_2) δ −115.04. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 85/15, flow = 0.7 mL/min, retention time 14.6 and 20.8 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{17}H_{19}FNO_4$ $[M + NH_4]^+$ 320.1293, found 320.1293.

*(+)-Ethyl 2-(4-chlorophenyl)-4-hydroxychromane-3-carboxylate (**2n**).* Reaction time: 21 h, 66 mg, 99% yield, white solid, mp = 214−215 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 5/1), 98% ee, $[\alpha]^{20}_D$ = +45.57 (*c* 1.22, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.7 Hz, 1H), 7.41−7.35 (m, 4H), 7.23−7.21 (m, 1H), 7.04 (td, *J* = 7.6, 1.1 Hz, 1H), 6.94 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.39 (d, *J* = 2.5 Hz, 1H), 5.26 (br, 1H), 3.95−3.90 (m, 2H), 3.48 (dd, *J* = 6.2, 2.5 Hz, 1H), 2.92 (d, *J* = 9.7 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 153.9, 137.0, 133.6, 129.1, 128.4, 127.2, 127.0, 124.7, 121.9, 116.2, 76.6, 66.7, 60.8, 50.5, 13.8. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 85/15, flow = 0.7 mL/min, retention time 14.0 and 23.3 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{18}H_{21}ClNO_4$ $[M + NH_4]^+$ 350.1154 (^{35}Cl) and 352.1131 (^{37}Cl), found 350.1152 (^{35}Cl) and 352.1116 (^{37}Cl).

*(+)-Ethyl 2-(4-bromophenyl)-4-hydroxychromane-3-carboxylate (**2o**).* Reaction time: 36 h, 70 mg, 93% yield, white solid, mp = 215−216 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 5/1), > 99% ee, $[\alpha]^{20}_D$ = +41.82 (*c* 1.04, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.25−7.21 (m, 1H), 7.05 (dd, *J* = 10.9, 4.0 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 5.37 (d, *J* = 2.2 Hz, 1H), 5.25 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.95- 3.90 (m, 2H), 3.48 (dd, *J* = 6.1, 2.5 Hz, 1H), 2.92 (d, *J* = 10.8 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 153.9, 137.6, 131.3, 129.1, 127.3, 127.2, 124.7, 121.9, 121.7, 116.3, 76.6, 66.7, 60.8, 50.4, 13.8. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 85/15, flow = 0.7 mL/min, retention time 14.5 and 25.0 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{18}H_{21}BrNO_4$ $[M + NH_4]^+$ 394.0648 (^{79}Br) and 396.0630 (^{81}Br), found 394.0631 (^{79}Br) and 396.0595 (^{81}Br).

*(−)-Cyclohexyl 2-cyclohexyl-4-hydroxychromane-3-carboxylate (**2p**).* Reaction time: 48 h, 59 mg, 82% yield, white solid, mp = 194−195 °C, new compound, R_f = 0.70 (hexanes/ethyl acetate 5/1), 98% ee, $[\alpha]^{20}_D$ = −71.00 (*c* 0.40, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.99 (dd, *J* = 10.5, 6.0 Hz, 1H), 4.90−4.80 (m, 1H), 3.81 (d, *J* = 9.7 Hz, 1H), 3.36 (d, *J* = 5.4 Hz, 1H), 3.01 (d, *J* = 11.0 Hz, 1H), 2.31 (d, *J* = 11.9 Hz, 1H), 2.03 (d, *J* = 11.9 Hz, 1H), 1.95−1.88 (m, 1H), 1.80−1.70 (m, 5H), 1.70−1.55 (m, 1H), 1.48−1.20 (m, 10H), 0.97−0.94 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 154.5, 128.6, 127.0, 125.6, 121.2, 115.8, 81.5, 73.3, 67.2, 45.5, 39.7, 31.5, 31.4, 30.2, 28.5, 26.4, 25.8, 25.6, 25.3, 23.3, 23.2. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.7 mL/min, retention time 15.9 and 17.0 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{22}H_{30}KO_4$ $[M + K]^+$ 397.1776, found 397.1779.

*(−)-Cyclohexyl 4-hydroxy-2-isopropylchromane-3-carboxylate (**2q**).* Reaction time: 48 h, 45 mg, 71% yield, white solid, mp = 148−150 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate 10/1), 99% ee, $[\alpha]^{20}_D$ = −131.10 (*c* 0.54, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7 Hz, 1H), 7.15−7.13 (m, 1H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.79 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.00 (dd, *J* = 9.1, 6.3 Hz, 1H), 4.89−4.81 (m, 1H), 3.71 (dd, *J* = 10.0, 1.7 Hz, 1H), 3.37 (dd, *J* = 6.1, 1.8 Hz, 1H), 3.03 (d, *J* = 10.7 Hz, 1H), 2.20−2.17 (m, 1H), 1.77−1.74 (m, 2H), 1.60−1.56 (m, 2H), 1.46−1.41 (m, 3H), 1.34−1.26 (m, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 154.5, 128.6, 127.0, 125.5, 121.2, 115.8, 82.6, 73.3, 67.2, 46.0, 31.4, 31.3, 30.6, 25.3, 23.3, 23.2, 20.1, 18.6. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 97/3, flow = 0.6 mL/min, retention time 18.8 min (major) and 20.2 min. HRMS (ESI-TOF) *m*/*z* calculated for $C_{19}H_{26}NaO_4$ $[M + Na]^+$ 341.1723, found 341.1715.

*(+)-Cyclohexyl 4-hydroxy-6-methoxy-2-phenylchromane-3-carboxylate (**2r**).* Reaction time: 48 h, 63 mg, 82% yield, white solid, mp = 133−135 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate 5/1), 98% ee, $[\alpha]^{20}_D$ = +18.89 (*c* 0.90, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 4.8, 4.3 Hz, 2H), 7.40−7.37 (m, 2H), 7.33-7.29 (m, 1H), 7.15 (dd, *J* = 3.0, 0.6 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 6.82−6.78 (m, 1H), 5.35 (d, *J* = 2.1 Hz, 1H), 5.24 (d, *J* = 3.7 Hz, 1H), 4.66−4.61 (m, 1H), 3.80 (s, 3H), 3.51 (dd, *J* = 6.2, 2.4 Hz, 1H), 3.05 (brs, 1H), 1.64−1.58 (m, 1H), 1.47−1.43 (m, 1H), 1.40−1.23 (m, 3H), 1.20−1.10 (m, 4H), 0.98−0.90 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.2, 154.4, 148.1, 138.5, 128.2, 127.7, 125.7, 125.5, 117.1, 115.5, 111.0, 77.2, 73.3, 67.3, 55.8, 50.6, 31.2, 30.9, 25.2, 23.2, 23.1. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 20.2 and 27.5 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{23}H_{26}NaO_5$ $[M + Na]^+$ 405.1672, found 405.1673.

*(+)-Cyclohexyl 4-hydroxy-6-methyl-2-phenylchromane-3-carboxylate (**2s**).* Reaction time: 48 h (Note: 1.0 equiv of *t*-BuOK was added.), 68 mg, 92% yield, white solid, mp = 113−114 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate 5/1), 99% ee, $[\alpha]^{20}_D$ = +19.18 (*c* 0.86, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 4.9, 4.3 Hz, 2H), 7.41−7.35 (m, 3H), 7.33−7.28 (m, 1H), 7.05−6.84 (m, 1H), 5.38 (d, *J* = 2.2 Hz, 1H), 5.24 (d, *J* = 6.0 Hz, 1H), 4.66−4.60 (m, 1H), 3.51 (dd, *J* = 6.2, 2.4 Hz, 1H), 2.93 (brs, 1H), 2.32 (s, 3H), 1.62−1.58 (m, 1H), 1.51−1.46 (m, 1H), 1.41−1.26 (m, 3H), 1.22−1.06 (m, 4H), 0.99−0.89 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.2, 152.0, 138.5, 130.8, 129.6, 128.2, 127.7, 127.3, 125.5, 124.6, 116.0, 77.0, 73.3, 67.0, 50.7, 31.2, 30.9, 25.2, 23.2, 23.1, 20.7. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 15.3 and 21.0 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{23}H_{26}NaO_4$ $[M + Na]^+$ 389.1723, found 389.1739.

*(+)-Cyclohexyl 7-bromo-4-hydroxy-2-phenylchromane-3-carboxylate (**2t**).* Reaction time: 24 h, 84 mg, 97% yield, white solid, mp = 212−213 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate 5/1), 99% ee, $[\alpha]^{20}_D$ = +48.60 (*c* 1.00, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.42 (m, 3H), 7.42−7.36 (m, 2H), 7.35−7.29 (m, 1H), 7.17−7.13 (m, 2H), 5.41 (d, *J* = 2.2 Hz, 1H), 5.20 (dd, *J* = 10.7, 6.2 Hz, 1H), 4.67−4.56 (m, 1H), 3.52 (dd, *J* = 6.2, 2.5 Hz, 1H), 2.94 (d, *J* = 10.8 Hz, 1H), 1.60−1.57 (m, 1H), 1.48−1.45 (m, 1H), 1.41−1.33 (m, 2H), 1.28−1.10 (m, 5H), 0.97−0.88 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.9, 154.9, 137.8, 128.4, 128.3, 127.9, 125.4, 124.8, 124.3, 121.9, 119.3, 77.4, 73.6, 66.7, 50.3, 31.2, 30.9, 25.1, 23.2, 23.1. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 93/7, flow = 0.7 mL/min, retention time 14.7 and 17.8 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{22}H_{27}BrNO_4$ $[M + NH_4]^+$ 448.1118 (^{79}Br) and 450.1101 (^{81}Br), found 448.1115 (^{79}Br) and 450.1087 (^{81}Br).

*(+)-Ethyl 4-hydroxy-7-methoxy-2-phenylchromane-3-carboxylate (**2u**).* Reaction time: 48 h, 61 mg, 94% yield, white solid, mp = 196−198 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate 2/1), 99% ee, $[\alpha]^{20}_D$ = +27.50 (*c* 0.63, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.6, 0.5 Hz, 1H), 7.45−7.42 (m, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.35−7.30 (m, 1H), 6.62 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 5.40 (s, 1H), 5.23 (dd, *J* = 10.7, 6.3 Hz, 1H), 3.97−3.86 (m, 2H), 3.79 (s, 3H), 3.48 (dd, J = 6.3, 2.5 Hz, 1H), 2.83−2.71 (m, 1H), 0.90 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100

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MHz, $CDCl_3$) δ 169.8, 160.4, 155.3, 138.5, 128.4, 128.2, 128.0, 125.6, 117.2, 108.8, 101.1, 77.6, 66.6, 60.7, 55.5, 50.9, 13.8. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 21.7 and 25.2 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{19}H_{21}O_5$ $[M + H]^+$ 329.1384, found 329.1372.

*(+)-Ethyl 4-hydroxy-5-methoxy-2-phenylchromane-3-carboxylate (**2v**).* Reaction time: 48 h, 40 mg, 61% yield, colorless viscous oil, new compound, R_f = 0.45 (hexanes/ethyl acetate 2/1), 97% ee, $[\alpha]^{20}_D$ = +40.00 (*c* 0.20, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.43 (m, 2H), 7.38−7.34 (m, 2H), 7.33−7.29 (m, 1H), 7.19 (t, *J* = 8.3 Hz, 1H), 6.71−6.65 (m, 1H), 6.53 (d, *J* = 8.2 Hz, 1H), 5.49 (d, *J* = 6.9 Hz, 1H), 5.35 (d, *J* = 2.7 Hz, 1H), 4.26 (d, *J* = 1.4 Hz, 1H), 4.02−3.94 (m, 2H), 3.90 (s, 3H), 3.51 (dd, *J* = 6.9, 2.8 Hz, 1H), 0.97 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.0, 158.5, 155.7, 138.2, 129.3, 128.5, 128.2, 126.0, 112.1, 110.2, 103.2, 76.4, 64.5, 60.4, 55.8, 50.1, 14.1. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 18.6 and 30.2 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{19}H_{21}O_5$ $[M + H]^+$ 329.1384, found 329.1372.

*Synthesis of (+)-3-(Hydroxymethyl)-2-phenylchroman-4-ol (**4**).* (+)-(2*R*,3*S*,4*R*)-Ethyl 4-hydroxy-2-phenylchromane-3-carboxylate (**2a**) (59.6 mg, 0.2 mmol) was dissolved in 1.0 mL of dry tetrahydrofuran and the solution was added dropwise at 0 °C to a stirred suspension of lithium aluminum hydride (16 mg, 0.4 mmol, 2.0 equiv) in dry ether (2.0 mL) under nitrogen. The mixture was allowed to warm to room temperature over 3 h and then was quenched by addition of saturated solution of potassium and sodium tartrate (5.0 mL). The product was extracted with ether and the organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under the reduced pressure. Then, the resultant mixture was purified by column chromatography on silica gel using hexanes/ethyl acetate as eluent to give the chiral diol product (+)-**4**. 41 mg, 80% yield, white solid, mp = 106- 108 °C, new compound, R_f = 0.10 (hexanes/ethyl acetate 5/1), 98% ee, $[\alpha]^{20}_D$ = +44.85 (*c* 0.68, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.45−7.39 (m, 4H), 7.35−7.31 (m, 1H), 7.26−7.21 (m, 1H), 7.03 (td, *J* = 7.5, 1.1 Hz, 1H), 6.93 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.39 (d, *J* = 5.5 Hz, 1H), 5.31 (d, *J* = 1.8 Hz, 1H), 3.86 (dd, *J* = 11.2, 9.4 Hz, 1H), 3.64 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.06 (brs, 1H), 2.70−2.65 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.5, 138.7, 128.9, 128.6, 127.8, 127.6, 125.3, 124.7, 121.5, 116.1, 77.9, 70.1, 59.1, 43.5. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 80/20, flow = 0.7 mL/min, retention time 8.2 and 9.3 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{16}H_{16}NaO_3$ $[M + Na]^+$ 279.0992, found 279.0999.

*Synthesis of (+)-Ethyl 4-acetoxy-2-phenylchromane-3-carboxylate (**5**).* To a solution of (+)-**2a** (59.6 mg, 0.2 mmol) in dichloromethane (2.0 mL) was added pyridine (20.6 mg, 26 μL, 0.26 mmol), 4-(dimethylamino)pyridine (5.0 mg, 0.04 mmol) and acetic anhydride (27.0 mg, 24 μL, 0.26 mmol) at 0 °C. Then, the mixture was allowed to warm to room temperature and stirred overnight. The solution was quenched with 3 M HCl aqueous solution (5.0 mL) and water (5.0 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), washed with brine, dried over sodium sulfate, filtered, and concentrated under the reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexanes/ethyl acetate = 15:1) to afford the desirable product (+)-**5**. 63 mg, 93% yield, colorless oil, new compound, R_f = 0.70 (hexanes/ethyl acetate 5/1), 99% ee, $[\alpha]^{20}_D$ = +14.68 (*c* 1.26, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 5.0, 3.9 Hz, 2H), 7.41- 7.30 (m, 3H), 7.26 (dt, *J* = 4.6, 1.2 Hz, 2H), 7.05−6.96 (m, 2H), 6.41 (d, *J* = 6.7 Hz, 1H), 5.46 (d, *J* = 2.7 Hz, 1H), 3.91 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.65 (dd, *J* = 6.7, 2.7 Hz, 1H), 2.14 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.9, 167.5, 154.8, 137.8, 129.4, 128.4, 128.2, 126.6, 125.8, 121.2, 120.3, 119.2, 116.5, 76.0, 67.5, 60.4, 47.5, 21.0, 13.9. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.7 mL/min, retention time 15.9 and 17.7 min (major). HRMS (ESI-TOF) *m*/*z* calculated for $C_{20}H_{24}NO_5$ $[M + NH_4]^+$ 358.1649, found 358.1640.

Scale-up Experiment. Under the nitrogen atmosphere, a mixture of ethyl 4-oxo-2-phenylchromane-3-carboxylate **1a** (1.037 g, 3.5 mmol) and RuCl[(*R*,*R*)-Tsdpen](*p*-cymene) catalyst **3a** (44.5 mg, 0.07 mmol) in an azeotrope of formic acid, triethylamine (5:2, 1.4 mL, 17.5 mmol), and *N*,*N*-dimethylformamide (DMF, 20 mL) was stirred at 40 °C for 24 h. After being cooled to ambient temperature, ethyl acetate (10 mL) was added, and then the organic phase was washed with water (3 × 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant mixture was subject to purification by column chromatography on silica gel (eluent: hexanes/ethyl acetate = 10:1, v/v) to afford the desired reductive product (+)-(2*R*,3*S*,4*R*)-**2a** 993 mg in 95% yield and 99% ee.

Determination of the Absolute Configuration of Compound (+)-2a. To determine the absolute configuration of (+)-ethyl-4-hydroxy-2-phenylchromane-3-carboxylate (**2a**): First, (+)-**2a** was upgraded to >99% ee by recrystallization with *n*-hexane/dichloromethane. Then, (+)-**2a** was completely dissolved in dichloromethane (1.0 mL), and *n*-hexane (2 mL) was added slowly at ambient temperature. The solvent was slowly evaporated, and the single crystal of (+)-**2a** was obtained after 3 days. The structure in Figure S1 showed the absolute configuration of (+)-**2a** is (2*R*,3*S*,4*R*). The CCDC number is 2014907. These details can be obtained free of charge via www.ccdc.com.ac.uk/data_request/cif from the Cambridge Crystallographic Data Centre.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00418.

Copies of ^{1}H, $^{13}C\{^1H\}$, and $^{19}F\{^1H\}$ NMR spectra of all new compounds (PDF)

Accession Codes

CCDC 2014907 contains 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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