JOC The Journal of Organic Chemistry

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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

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Cite This: J. Org. Chem. 2021, 86, 4849–4858 Read Online

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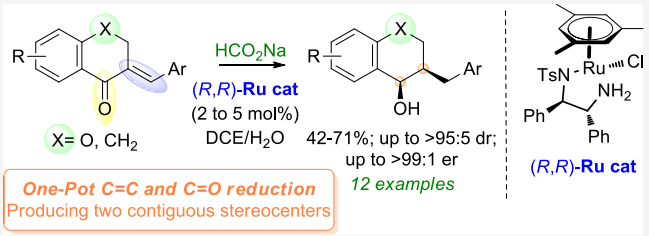
ABSTRACT: 3-Arylidenechroman-4-ones and 2-arylidene-1-tetralones are hydrogenated to *cis*-benzylic alcohols in dr's and er's up to 99:1 via a C=C and C=O one-pot reduction in the presence of 2–5 mol % Noyori–Ikariya-type Ru^{II} chiral complexes and HCO_2Na as a hydrogen source under asymmetric transfer hydrogenation–dynamic kinetic resolution (ATH-DKR) conditions. The oxidation of theses substrates resulted in the enantioselective synthesis of the natural homoisoflavanone dihydrobonducellin and its carba-analogues.



The asymmetric transfer hydrogenation (ATH) of carbonyl compounds catalyzed by chiral transition-metal complexes is a powerful tool for obtaining key intermediates in the synthesis of optically pure pharmaceutical and natural products.[1−10] The Noyori–Ikariya-type Ru^{II} complexes (**1a**–**e**) (Figure 1) have been used in water and organic solvents to promote the ATH of pro-chiral C=O and C=N groups in high ee's.[11−20]

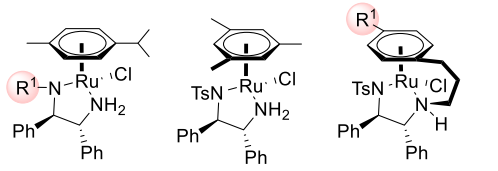


Figure 1. η^6-Arene-*N*-arylsulfonyldiamine Ru^{II} complexes **1a**–**e**.

Concerning the ATH of enones, allylic alcohols are usually formed using these catalysts.[21−26] Deng et al.[27] reported the reduction of α,β-unsaturated methyl ketones to allylic alcohols using (*R*,*R*)-**1a** (Scheme 1a). However, the reduction of chalcone was an exception, resulting in the saturated ketone as the major product (75%) along with the corresponding benzylic alcohol (23%) in a 93% ee. Just recently, Wills et al.[28] reported the preferential 1,4-reduction of chalcones, which was promoted by (*R*,*R*)-**1e** and a HCO_2H/Et_3N mixture (Scheme 1b).

The enantioselective synthesis of homoisoflavanones through an asymmetric transfer hydrogenation–dynamic kinetic resolution (ATH-DKR) reaction catalyzed by (*R*,*R*)-**1a** was reported by Seo et al. in two works[29,30] (Scheme 1c). First, the exocyclic C=C bond in arylidenechromanones was reduced by hydrogenation with Pd/C, followed by the ATH-DKR of the resulting saturated ketones using a large catalytic loading of (*R*,*R*)-**1a** (30 mol %) and a HCO_2H/DBU mixture.

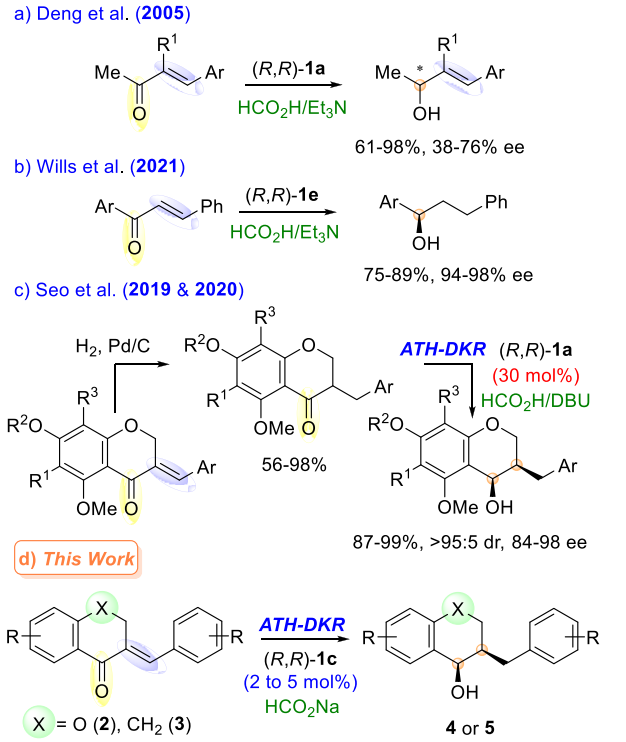
Therefore, we envisioned that the C=C and C=O bonds in arylidene-substituted chromanones (**2**) and tetralones (**3**) could be reduced by (*R*,*R*)-**1** through an one-pot procedure to the corresponding saturated benzylic alcohols (Scheme 1d), avoiding the previous step of the hydrogenation of the C=C bond.[31−36] Xiao discloses that when HCO_2Na is used as the hydrogen source instead of HCO_2H/Et_3N at a pH around 7, much faster rates and higher turnover numbers can be delivered with (*R*,*R*)-**1** in the ATH of ketones without significative losses of ee.[37−41] This trend was also found in our preliminary screening of the hydrogen source for the ATH. Only traces of the saturated alcohol were obtained for the more deactivated substrates using HCO_2H/Et_3N mixtures (Table S1).

The hydrogenation of enone **2a** using 5 equiv of HCO_2Na in water with 5 mol % (*R*,*R*)-**1a** and 20 mol % of cationic cetyltrimethylammonium bromide (CTAB) as phase-transfer catalyst (PTC) at 45 °C (Table 1, entry 1) led, after 20 h, to a

Received: December 19, 2020
Published: March 8, 2021

https://dx.doi.org/10.1021/acs.joc.0c02981
J. Org. Chem. 2021, 86, 4849–4858

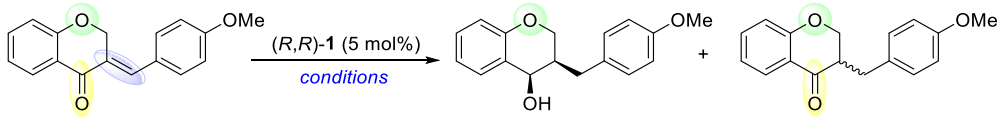
Scheme 1. ATH of α,β-Unsaturated Ketones Using (*R,R*)-1 Catalysts



mixture of **4a** and **6a**, showing that the catalyst was able to promote the total reduction of the enone through a DKR process and resulting the *cis*-**4a** alcohol with an (*R,R*)-configuration as the major product.[30] In methanol (Table 1, entry 2) the full conversion of the intermediate **6a** was observed (as for all other entries in Table 1) and **4a** was formed with a higher enantioselectivity (97:3 er), but the *cis*/*trans* ratio remained the same (72:28). In MeOH/H_2O, the *cis*/*trans* ratio decreased (Table 1, entry 3), while DCE/H_2O improved the diastereoselectivity to 82:18 but with a decrease in the er (Table 1, entry 4). Attempts to improve the stereoselectivity in DCE/H_2O resulted in tests with neutral and anionic PTC (Table 1, entries 5 and 6, respectively; see also Table S2) as well as tests under acid and basic conditions using, respectively, HCO_2H and Na_2CO_3 as additives (Table 1, entries 7 and 8, respectively); however, no significant improvements were achieved. The decrease in the reaction time from 20 to 5 h did not affect the conversion of **2a** (compare Table 1, entries 4 and 9, respectively), but an increase in the stereoselectivity was observed.

Then, the precatalysts (*R,R*)-**1b−d** were tested under the same conditions (Table 1, entries 10−12, respectively). A better er was found in all cases compared to that with (*R,R*)-**1a**. However, despite the excellent er achieved by (*R,R*)-**1d** (>99:1), a significant loss of diastereoselectivity was observed (Table 1, entry 12). Thus, (*R,R*)-**1c** was considered the best complex (92:8 *cis*/*trans*, 95:5 er). The efficacy of this η^6-mesitylene precatalyst was already reported due to its ability to form multiple electrostatic CH−π interactions with the substrate.[42] A decrease in the temperature from 45 °C to rt showed no effect on the reaction stereoselectivity (Table 1, entry 13). Finally, Lewis acids and Brønsted acids were used as additives[43−45] (Table S3), and 10 mol % $Cu(OTf)_2$ resulted in

Table 1. Optimization of ATH-DKR Conditions for 2a[a]



2a (*cis*)-**4a** **6a**

entry	(*R,R*)-**1**	*T* (°C)	*t* (h)	PTC[b]	solvent[c]	additive[d]	**4a**/**6a**[e]	**4a** *cis*/*trans*[e]	yield (%)[f]	er (%)[g]
1	**1a**	45	20	CTAB	H_2O		73:27	72:28	34	93:7
2	**1a**	45	20	CTAB	MeOH		>95:5	72:28	54	97:3
3	**1a**	45	20	CTAB	MeOH/H_2O		>95:5	62:38	57	95:5
4	**1a**	45	20	CTAB	DCE/H_2O		>95:5	82:18	71	88:12
5	**1a**	45	20	Tween 20	DCE/H_2O		>95:5	81:19	66	89:11
6	**1a**	45	20	OSAS	DCE/H_2O		>95:5	85:15	83	85:15
7	**1a**	45	20	CTAB	DCE/H_2O	HCO_2H	>95:5	74:26	72	73:27
8	**1a**	45	20	CTAB	DCE/H_2O	Na_2CO_3	>95:5	80:20	72	89:11
9	**1a**	45	5	CTAB	DCE/H_2O		>95:5	86:14	73	92:8
10	**1b**	45	5	CTAB	DCE/H_2O		>95:5	74:26	74	95:5
11	**1c**	45	5	CTAB	DCE/H_2O		>95:5	92:8	85	95:5
12	**1d**	45	5	CTAB	DCE/H_2O		>95:5	62:38	60	>99:1
13	**1c**	rt	20	CTAB	DCE/H_2O		>95:5	92:8	69	95:5
14	**1c**	45	5	CTAB	DCE/H_2O	$Cu(OTf)_2$	>95:5	90:10	66	97:3
15	**1c**	rt	20	CTAB	DCE/H_2O	$Cu(OTf)_2$	>95:5	90:10	65	98:2

[a]All reactions were carried out on a 0.1 mmol scale using (*R,R*)-**1** (5 mol %) and HCO_2Na (5 equiv). [b]PTC (phase-transfer catalyst, 20 mol %): CTAB, cetyltrimethylammonium bromide; Tween 20, polyoxyethylenesorbitan monolaurate; and OSASS, octane-1-sulfonic acid sodium salt. [c]At 0.25 M using the pure solvent or a 1:1 mixture with water. [d]Using HCO_2H (5 equiv), Na_2CO_3 (1.25 equiv), and $Cu(OTf)_2$ (10 mol %) when specified. [e]Ratios were determined by the analysis of the ^1H NMR spectrum of the crude mixture. The full conversion of **2a** was achieved in all tests except entry 2 (63%). The corresponding allylic alcohol was found as a minor product (<5%) in entries 1, 3, 9, 11, and 15. [f]Isolated yield for the major diastereoisomer (*cis*-**4a**) after preparative TLC. [g]Determined by HPLC analysis using a chiral stationary phase column for the major diastereoisomer.

https://dx.doi.org/10.1021/acs.joc.0c02981
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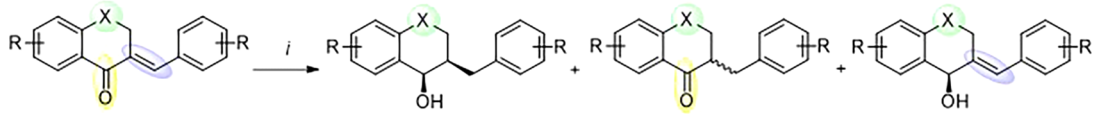
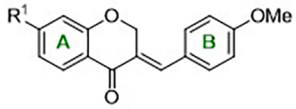
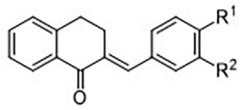
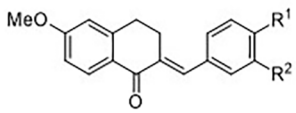
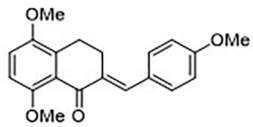
Table 2. Scope of the ATH-DKR of 2 and 3 Catalyzed by (*R,R*)-1c[a]



i = (*R,R*)-**1c** , HCO_2Na, $Cu(OTf)_2$, CTAB, DCE/H_2O, rt, 20 h (**2**) or 72 h (**3**)

entry	arylenones 2 or 3		R^1	R^2	4:6:8 or 5:7:9[b]	4 or 5 *cis/trans*[b]	*cis*-4 or *cis*-5 yield (%)[c]	*cis*-4 or *cis*-5 er (%)[d]
1		**2b**	OMe		85:15:0	>95:5	61	97:3
2		**2c**	OMOM		91:9:0	>95:5	71	99:1
3		**2d**	OAc		92:0:9	77:23	63	93:7
4		**3a**	H	H	73:8:19	88:12	53	92:8
5		**3b**	Cl	H	83:4:13	>95:5	75	91:9
6		**3c**	OMe	H	74:10:16	>95:5	52	98:2
7		**3d**	OMe	OMe	78:15:7	>95:5	59	98:2
8		**3e**	H	H	61:35:4	>95:5	51	98:2
9		**3f**	OMe	H	63:34:3	>95:5	48	97:3
10		**3f**[e]	OMe	H	73:27:0	94:6	59	95:5
11		**3g**	OMe	OMe	71:29:0	>95:5	44	>99:1
12		**3h**			65:30:5	>95:5	42	99:1

[a]All reactions were carried out on a 0.1 mmol scale using (*R,R*)-**1c** (5 mol %), HCO_2Na (5 equiv), $Cu(OTf)_2$(10 mol %), CTAB (20 mol %), and DCE/H_2O (1:1, 0.25 M) at rt for either 20 (**2a−d**) or 72 h (**3a−h**). [b]Determined by the analysis of the ^1H NMR spectrum of the crude mixture; conversions ≥95% were achieved. [c]Isolated yield for the major diastereoisomer (*cis*-**4**/**5**) after preparative TLC. [d]Determined by HPLC analysis for the major diastereoisomer. [e]At 45 °C for 20 h.

a good increase of the er from 95:5 to 98:2 for the ATH-DKR of **2a** compared to tests without the additive at 45 °C or rt (Table 1, compare entries 10 and 13 against 14 and 15).

Next, the hydrogenation of different homoisoflavones **2b−d** was also investigated (Table 2, entries 1−3, respectively). These substrates were oxygenated at the 7-position of the A-ring with different protecting groups, which could be removed after an oxidative step of the resulting alcohols **4b−d** to enantioselectively obtain the natural homoisoflavanone dihydrobonducellin (**10c**). The electron-donating groups in **2b** (OMe) and **2c** (OMOM) decreased the substrate reactivity, and the intermediate ketones **6b** and **6c** were found in the reaction crude in 15 and 9% yields, respectively, after 20 h. Moreover, to our delight higher diastereoselectivities (>95:5) and excellent er's (up to 99:1) were achieved in alcohols **4b** and **4c**. In contrast, the reaction with **2d** (7-OAc) resulted in a decrease in the reaction stereoselectivity, and 9% of the allylic alcohol **8d** was also formed (Table 2, entry 3).

The substitution of the oxygen atom at the chromanone ring by the methylene group in enones **3a−h** significantly decreases the chemical reactivity (Table 2). Therefore, the reaction times were set at 72 h at rt to achieve higher conversions rates. Interestingly, the lower reactivity of these substrates resulted in alcohols *cis*-**5** as major products in high diastereo- and enantioselectivities. For substrates unsubstituted at the A-ring (**3a−d**) (Table 2, entries 4−7, respectively), considerable amounts of allylic alcohols **9a−d** were obtained with high enantioselectivities, for instance, **9b** with a 96:4 er. The decrease in the reactivity was even more pronounced in enones substituted by methoxy groups on the A-ring in the *para*- or *ortho*-position to the carbonyl group (Table 2, entries 8−12), resulting in 29−35% yields of ketones **7e−h** in the same reaction time. Interestingly, in these cases only small amounts of allylic alcohols **8e−h** were formed in the crude reaction. With the aim of improving the chemical yields of alcohols *cis*-**5**, additional tests were performed with the enone **3f**. With the increase in temperature from rt to 45 °C, the alcohol *cis*-**5f** was isolated in a 59% yield in 20 h at a similar level of stereoselectivity (Table 2, entry 10), while a 48% yield was found after 72 h at rt (Table 2, entry 9). Besides, the beneficial effect of $Cu(OTf)_2$ over the reaction outcome could be proven again, since without the additive the enantioselectivity dropped to an 89:11 ratio at 45 °C (Table S6).

The alcohols *cis*-**4a** and *cis*-**5c**, which were obtained through reduction with the (*S,S*)-**1c** catalyst, were oxidized to ketones (*S*)-**6a** and (*R*)-**7c** using Dess−Martin periodinane (DMP)

https://dx.doi.org/10.1021/acs.joc.0c02981
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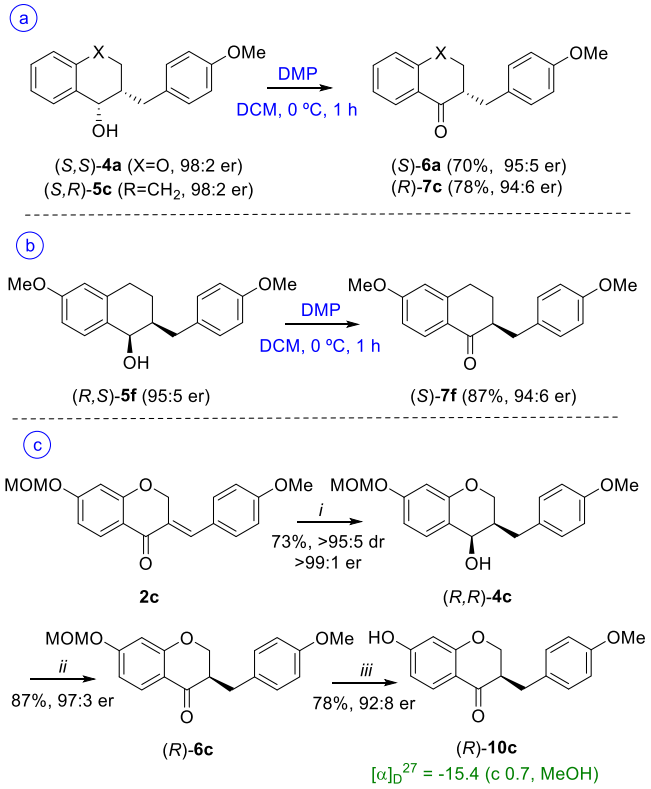
without an erosion of the ee (Scheme 2a).[46] Next, (*R*,*S*)-**5f** was also oxidized under the same reaction conditions, resulting in

Scheme 2. Enantioselective Synthesis of Homoisoflavanones and Carba-Analogues



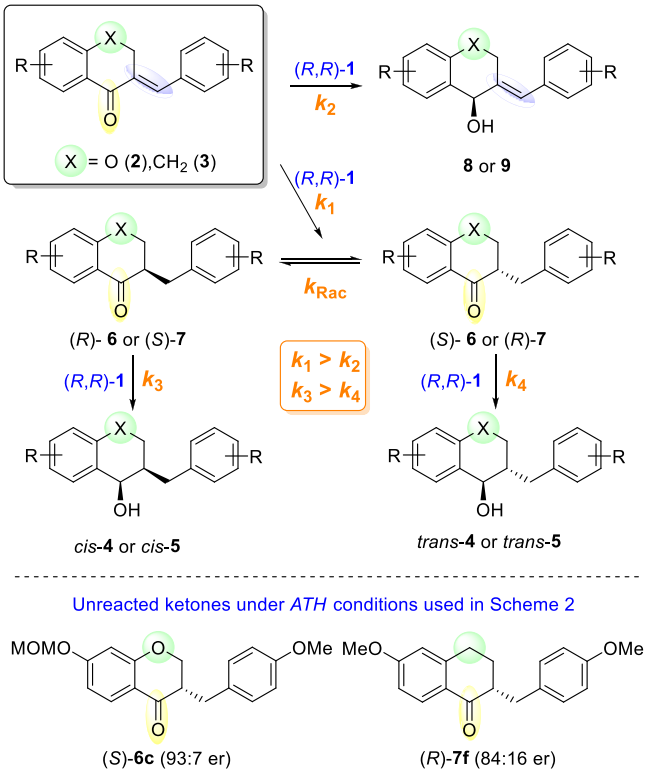
i = (*R*,*R*)-**1c** (2 mol%), $Cu(OTf)_2$ (4 mol%), HCO_2Na, CTAB, DCE/H_2O, rt, 20 h; *ii*= DMP, DCM, 0 °C, 1 h; *iii* =$ZnBr_2$, *n*BuSH, DCM, 0 °C, 1 h

(*S*)-**7f** in a 94:6 er (Scheme 2b). This ketone belongs to a family of synthetic compounds that displays antiproliferative activity against MCF-7 tumor cells.[47] Then, for the synthesis of the natural dihydrobonducellin,[48] the arylenone **2c** was reduced in an excellent dr and er to alcohol (*R*,*R*)-**4c** using only 2 mol % precatalyst (*R*,*R*)-**1c** at rt for 20 h. After an oxidation step to (*R*)-**6c**, followed by MOM removal under mild conditions,[49] (*R*)-**10c**[48] was obtained with a 50% overall yield and a 92:8 er. (Scheme 2c).

Once **8** or **9** were present in some of our crude products and the transformation of allylic alcohols into enantiomeric-enriched saturated alcohols was reported using Ru^{II} complexes, we considered that these alcohols could be the precursors of saturated alcohols **4** and **5**.[50−53] To check this possibility, the allylic alcohols (*rac*)-**8a** and (*rac*)-**9c** were prepared by the reduction of **2a** and **3a**, respectively, with $NaBH_4$ and submitted to the same reaction conditions at rt. Interestingly, these allylic alcohols did not lead to saturated alcohols **4a** and **5c** (Scheme S1). Therefore, we assume that the ratio between the saturated alcohols and the allylic alcohols observed in our reactions reflects the relative rate of 1,4- vs 1,2-addition in the first step of the reduction of enones **2** or **3**.

All these results (Tables 1 and 2) are in agreement with the mechanistic proposal showed in Scheme 3. In the first step, enones **2** or **3** are hydrogenated to ketones **6** or **7** (1,4-reduction), respectively, and the resulting enantiomers are in equilibrium through the enol tautomers. This step is faster than

Scheme 3. Mechanistic Proposal for the Reductions of 2 and 3



the 1,2-reduction that leads to allylic alcohols **8** or **9**. The resulting ketones **6** or **7** are reduced through DKR to the saturated alcohols *cis*-**4** or *cis*-**5**, respectively, as major products.

Interestingly, nonconsumed ketones **6c** (Table 2, entry 2) and **7f** (Table 2, entry 10) were not racemic but instead enantiomerically enriched with their less-reactive enantiomers (*S*)-**6c** and (*R*)-**7f**, respectively. These er's are the result of the combination of the rate of the enantiomer interconversion and the rate of the consumption (*R*)-**6** and (*S*)-**7** to the corresponding *cis*-alcohols *cis*-**4** and *cis*-**5**. On the other hand, alcohols *trans*-**4** or *trans*-**5** would originate from (*S*)-**6** or (*R*)-**7**.

In conclusion, the Ru^{II} chiral complex (*R*,*R*)-**1c** acts as dual precatalyst in the total reduction of enones **2** and **3** through the reduction of C=C bonds, followed by ATH-DKR of the resulting saturated ketones. By using low catalyst loadings (2−5 mol %) in a biphasic aqueous media under neutral conditions, the isolated yields ranged from moderate to high with high diastereo- and enantiomeric ratios. Finally, the developed protocol proved to be practical and suitable for a scaled-up reaction (Scheme S3). Additional mechanistic studies, synthetic applications, and the antiproliferative activity evaluation of the synthesized compounds are under investigation in our laboratories.

EXPERIMENTAL SECTION

General Information. All commercially available reagents and solvents were used without further purification. The (*R*,*R*)-**1a−d** precatalysts were purchased from Sigma-Aldrich. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60 F_{254} plates and visualized either under UV light (254 or 365 nm) or by staining with vanillin/H_2SO_4. Preparative TLC was performed on 20 cm × 20 cm glass-backed plates bearing a 0.5 mm layer of silica gel 60 F_{254}(15−40 μm). Flash column chromatography was performed on

https://dx.doi.org/10.1021/acs.joc.0c02981
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silica gel 60 (230−400 mesh) SiliaFlash. Optical rotations were measured on a Jasco P-2000 polarimeter at approximately 27 °C, and concentrations (c) are given in grams per 100 mL. Enantiomeric excesses were determined using a Shimadzu LC 20AT Prominence HPLC system equipped with a UV detector (SPD-M20A), a system controller (CBM-20A), a column oven (CTO-20A), an autosampler (SIL-20AHT), an online degasser (DGU-20A), and a chiral column (CHIRALPAK-IA) using mixtures of *n*-hexane/isopropyl alcohol as the mobile phase at 28 °C. NMR spectra were recorded on Varian Unity 400 and 500 MHz instruments at 25 °C. Chemical shifts are expressed in ppm relative to TMS or the deuterated solvent, and the coupling constants (*J*) are expressed in Hertz. High-resolution mass spectra were obtained with a Bruker Maxis Impact mass spectrometer with an eletrospray ionization (ESI) source coupled to quadrupole Time-Of-Flight (qTOF) hybrid mass analyzer.

Preparation of the Compounds. *(E)-3-(4-Methoxybenzylidene)chroman-4-one (**2a**).*[54] 4-Chromanone (1.0 mmol, 148 mg) was dissolved in methanol (6 mL), followed by the addition of 4-methoxybenzaldehyde (1.05 mol, 128 μL) and concentrated hydrochloric acid (3 mL). The mixture was refluxed for 24 h and then diluted with water. Filtration afforded the crude product, which was crystallized from methanol to give **2a** as a pure product (215 mg, 81% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.84 (s, 1H), 7.48 (ddd, *J* = 8.3, 7.2, 1.8 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.07 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 7.00−6.94 (m, 3H), 5.38 (d, *J* = 1.8 Hz, 2H), 3.86 (s, 3H).

Synthesis of 7-Hydroxy-chromanon-4-one.[55] *Step 1.* The trifluoromethanesulfonic acid (24 mmol, 2.12 mL) was added to a mixture of Resorcinol (8 mmol, 881 mg) and 3-chloropropionic acid (9.6 mmol, 1042 mg). The resulting solution was stirred at 80 °C for 1 h, cooled to room temperature over 10 min, and poured into chloroform (50 mL). Then, the solution was washed with water (50 mL x 2), and the aqueous layer was extracted with chloroform (25 mL × 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting product 3-chloro-1-(2,4-dihydroxyphenyl) propan-1-one (911 mg, 56% yield) was used crude in the next step: ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.46 (s, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 6.41 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 5.46 (s, 1H), 3.91 (t, *J* = 6.8 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H). *Step 2.* A NaOH solution (2 M, 40 mL) was added to a round-bottom flask containing 3-chloro-1-(2,4-dihydroxyphenyl) propan-1-one (4.5 mmol, 903 mg), and the resulting mixture was left under stirring at rt for 2 h. Then, a H_2SO_4 solution (6 M) was added until pH < 2, and the mixture was extracted with AcOEt (60 mL × 2). The resulting organic phase was washed with brine (120 mL), dried over Na_2SO_4, and concentrated under reduced pressure, resulting in 7-hydroxy-chroman-4-one (705 mg, 54% yield for the two steps) that was used without further purification in the following step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.7 Hz, 1H), 6.52 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.03 (s, 1H), 4.51 (t, *J* = 6.4 Hz, 2H), 2.82−2.71 (m, 2H).

(E)-7-Hydroxy-3-(4-methoxybenzylidene)chroman-4-one.[56] 7-hydroxy-chroman-4-one (1.0 mmol, 164 mg) was dissolved in methanol (6 mL) followed by the addition of 4-methoxybenzaldehyde (1.05 mol, 128 μL) and concentrated hydrochloric acid (3 mL). The mixture was refluxed for 24 h and then diluted with water. Filtration afforded the crude product, which was crystallized from methanol to give the pure product (175 mg, 62% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.65 (s, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.64 (s, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.55 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.32 (d, *J* = 2.1 Hz, 1H), 5.36 (d, *J* = 1.6 Hz, 2H), 3.82 (s, 3H).

*(E)-7-Methoxy-3-(4-methoxybenzylidene)chroman-4-one (**2b**).*[57] To a solution of (*E*)-7-hydroxy-3-(4-methoxybenzylidene)chroman-4-one (1 mmol, 282 mg) in acetone (5 mL) at rt were added iodomethane (3 mmol, 0.19 mL) and K_2CO_3 (3 mmol, 415 mg). The mixture was refluxed for 2 h, then the acetone was evaporated, and the crude was diluted in AcOEt (25 mL). The mixture was washed with water (25 mL) and brine (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure, resulting in **2b** (240 mg, 81% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.31−7.23 (m, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.63 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 5.36 (d, *J* = 2.0 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H).

*(E)-3-(4-Methoxybenzylidene)-7-(methoxymethoxy)chroman-4-one (**2c**).*[58] To a solution of (*E*)-7-hydroxy-3-(4-methoxybenzylidene)chroman-4-one (1 mmol, 282 mg) in dry DCM (4 mL) at 0 °C under an argon atmosphere was added DIPEA (3 mmol, 0.52 mL). After stirring for 10 min, MOMCl (3 mmol, 0.23 mL) was added to the solution dropwise. The resulting mixture was stirred for 16 h at rt. Afterward, the solution was poured into saturated aq NH_4Cl (30 mL), then DCM (30 mL) was added to the mixture. The organic layer was washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by flash chromatography (*n*-hexane/AcOEt 75:25) to afford the pure product as a yellow solid (222 mg, 68% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.79 (s, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.00−6.92 (m, 2H), 6.71 (ddd, *J* = 8.8, 2.4, 1.0 Hz, 1H), 6.58 (t, *J* = 1.6 Hz, 1H), 5.34 (s, 2H), 5.19 (s, 2H), 3.83 (s, 3H), 3.47 (s, 3H).

*(E)-3-(4-Methoxybenzylidene)-4-oxochroman-7-yl acetate (**2d**).*[59] To a MW tube equipped with a standard cap (CEM Discover) were added (*E*)-7-hydroxy-3-(4-methoxybenzylidene)-chroman-4-one (1 mmol, 282 mg), pyridine (2 mL), and acetic anhydride (8 mmol, 882 μL). The tube was sealed, and the sample was irradiated at 100 °C for 1 h. Then, methanol (10 mL) was added at rt to remove the acetic anhydride under reduced pressure. Toluene (10 mL × 4) was added and evaporated to remove the pyridine. Finally, methanol (10 mL × 4) was added and evaporated off to remove the remaining toluene, resulting in **2d** (279 mg, 86% yield) as a light-yellow solid that was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.6 Hz, 1H), 7.84 (s, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.81 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.76 (d, *J* = 2.1 Hz, 1H), 5.40 (d, *J* = 1.6 Hz, 2H), 3.87 (s, 3H), 2.31 (s, 3H).

General Procedure for the Synthesis of 3a−g.[60] The corresponding 1-tetralone (1.0 mmol) was dissolved in ethanol (6 mL), followed by the addition of the appropriate benzaldehyde (1.0 mol). The 10% aq solution of NaOH was added dropwise to the mixture at 0 °C. After 20 min, the mixture was stirred for 24 h at room temperature. Filtration afforded the products **3a−h** as pure products.

*(E)-2-Benzylidene-3,4-dihydronaphthalen-1(2H)-one (**3a**).*[61] Yielded 221 mg, 94%: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.54−7.32 (m, 6H), 7.29−7.21 (m, 2H), 3.14 (ddd, *J* = 6.8, 5.6, 1.8 Hz, 2H), 2.95 (dd, *J* = 7.5, 5.4 Hz, 2H).

*(E)-2-(4-Chlorobenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**3b**).*[62] Yielded 215 mg, 80%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.68 (s, 1H), 7.37 (td, *J* = 7.5, 1.5 Hz, 1H), 7.30−7.20 (m, 5H), 7.13 (d, *J* = 7.6 Hz, 1H), 2.97 (td, *J* = 6.5, 1.9 Hz, 2H), 2.83 (dd, *J* = 7.6, 5.3 Hz, 2H).

*(E)-2-(4-Methoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**3c**).*[63] Yielded 240 mg, 91%: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.85 (s, 1H), 7.48 (td, *J* = 7.5, 1.4 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 3.15 (td, *J* = 6.5, 1.8 Hz, 2H), 2.95 (t, *J* = 6.5 Hz, 2H).

*(E)-2-(3,4-Dimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**3d**).*[64] Yielded 183 mg, 62%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.8 Hz, 1H), 7.84 (s, 1H), 7.49 (tt, *J* = 7.5, 1.1 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.28−7.22 (m, 1H), 7.13−7.06 (m, 1H), 6.99 (d, *J* = 1.9 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.21−3.14 (m, 2H), 2.96 (t, *J* = 6.5 Hz, 2H).

*(E)-2-Benzylidene-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**3e**).*[65] Yielded 154 mg, 58%: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.7 Hz, 1H), 7.84 (s, 1H), 7.47−7.31 (m, 5H), 6.88 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.71 (d, *J* = 2.5 Hz, 1H), 3.88 (s, 3H), 3.12 (ddd, *J* = 6.9, 5.7, 1.8 Hz, 2H), 2.97−2.89 (m, 2H).

https://dx.doi.org/10.1021/acs.joc.0c02981
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*(E)-6-Methoxy-2-(4-methoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**3f**).*[66] Yielded 138 mg, 47%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.7 Hz, 1H), 7.81 (s, 1H), 7.41 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.87 (dd, J = 8.7, 2.5 Hz, 1H), 6.70 (d, J = 2.5 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.12 (ddd, J = 6.9, 5.8, 1.8 Hz, 2H), 2.91 (dd, J = 7.6, 5.5 Hz, 2H).

*(E)-2-(3,4-Dimethoxybenzylidene)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**3g**).*[66] Yielded 84 mg, 26%: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.7 Hz, 1H), 7.80 (s, 1H), 7.11−7.03 (m, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.88 (dd, J = 8.7, 2.6 Hz, 1H), 6.71 (d, J = 2.5 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.14 (ddd, J = 7.0, 5.8, 1.8 Hz, 2H), 2.92 (t, J = 6.5 Hz, 2H).

*(E)-5,8-Dimethoxy-2-(4-methoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**3h**).*[53] 5,8-Dimethoxy-1-tetralone (1.0 mmol, 206 mg) was dissolved in methanol (6 mL), followed by the addition of 4-methoxybenzaldehyde (1.05 mol, 128 μL) and concentrated hydrochloric acid (3 mL). The mixture was refluxed for 24 h and then diluted with water. Filtration afforded the crude product, which was crystallized from methanol to give **3h** as a pure product (234 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 9.1 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 9.0 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 2.99 (ddd, J = 6.8, 5.3, 1.8 Hz, 2H), 2.86 (dd, J = 7.7, 5.1 Hz, 2H).

General Procedure for the Synthesis of (*R*,*R*)-4 or (*R*,*S*)-5. To a Pyrex tube were added the substrate **2** or **3** (0.1 mmol), RuCl[(*R*,*R*)-TsDPEN](mesitylene) **1c** (0.005 mmol, 3.1 mg), $Cu(OTf)_2$ (0.010 mmol, 3.6 mg), CTAB (0.020 mmol, 7.3 mg), and dichloroethane (0.2 mL), and the resulting mixture was stirred at rt for 15 min under an argon atmosphere. Then, a solution of sodium formate (0.5 mmol, 34 mg) in water (0.2 mL) was added, and the reaction mixture was stirred at room temperature for either 20 (**2a**−**d**) or 72 h (**3a**−**i**), diluted in AcOEt (10 mL), dried over Na_2SO_4 ,and filtered through a small pad of silica. The resulting crude was then purified by preparative thin-layer chromatography (in *n*-Hexane/AcOEt), yielding the pure products (*R*,*R*)-**4** or (*R*,*S*)-**5**.

*(3R,4R)-3-(4-Methoxybenzyl)chroman-4-ol (cis-**4a**).* All spectra were in agreement with reported data.[67] Purified by PTLC (*n*-hexane/EtOAc 75:25) as a white solid (18 mg, 65% yield): $[\alpha]_D^{27}$ = +30.2 (c = 1, $CHCl_3$); the enantiomeric ratio (98:2 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 10.6 min, t_{Rmin} = 14.6 min, 284 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23−7.16 (m, 4H), 6.91−6.82 (m, 4H), 4.50 (d, J = 3.1 Hz, 1H), 4.12−4.04 (m, 2H), 3.80 (s, 3H), 2.82 (dd, J = 13.8, 8.5 Hz, 1H), 2.62 (dd, J = 13.8, 7.3 Hz, 1H), 2.28 (ttd, J = 8.6, 7.2, 3.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.2, 154.5, 131.2, 130.3, 130.1, 123.0, 124.3, 120.6, 117.0, 114.1, 65.1, 65.0, 55.4, 40.2, 32.0; HRMS(ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{18}O_3Na^+$ 293.1148, found 293.1149.

*(3R,4R)-7-Methoxy-3-(4-methoxybenzyl)chroman-4-ol (cis-**4b**).* Purified by PTLC (*n*-hexane/AcOEt 70:30) as a light brown waxy solid (18 mg, 61% yield): $[\alpha]_D^{27}$ = +37.0 (c = 1, $CHCl_3$); the enantiomeric ratio (97:3 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 16.8 min, t_{Rmin} = 26.1 min, 284 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.5 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.47 (dd, J = 8.4, 2.5 Hz, 1H), 6.37 (d, J = 2.5 Hz, 1H), 4.45 (d, J = 3.0 Hz, 1H), 4.09−4.03 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 2.81 (dd, J = 13.8, 8.5 Hz, 1H), 2.61 (dd, J = 13.8, 7.2 Hz, 1H), 2.30−2.20 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.1, 158.2, 155.5, 131.2, 131.1, 130.1, 117.0, 114.1, 107.9, 101.3, 65.2, 64.6, 55.5, 55.4, 40.4, 32.2; HRMS(ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{20}O_4Na^+$ 323.1254, found 323.1257.

*(3R,4R)-3-(4-Methoxybenzyl)-7-(methoxymethoxy)chroman-4-ol (cis-**4c**).* Purified by PTLC (*n*-hexane/EtOAc 70:30) as a pale yellow oil (23 mg, 71% yield): $[\alpha]_D^{27}$ = +59.5 (c = 1, $CHCl_3$); the enantiomeric ratio (99:1 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol (90:10, 1 mL/min), t_{Rmaj} = 18.4 min, t_{Rmin} = 28.1 min, 284 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.5 Hz, 2H), 6.58 (dd, J = 8.4, 2.5 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 5.12 (s, 2H), 4.45 (d, J = 3.0 Hz, 1H), 4.09−4.03 (m, 2H), 3.80 (s, 3H), 3.45 (s, 3H), 2.80 (dd, J = 13.8, 8.5 Hz, 1H), 2.61 (dd, J = 13.8, 7.2 Hz, 1H), 2.29−2.20 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.4, 158.1, 155.3, 131.1, 131.0, 130.0, 118.2, 113.9, 109.1, 104.1, 94.3, 65.1, 64.5, 56.0, 55.4, 40.2, 32.0; HRMS(ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{22}O_5Na^+$ 353.1359, found 353.1360.

*(3R,4R)-4-Hydroxy-3-(4-methoxybenzyl)chroman-7-yl Acetate (cis-**4d**).* Purified by PTLC (*n*-hexane/EtOAc 70:30) as a pale yellow oil (21 mg, 63% yield): $[\alpha]_D^{27}$ = +29.9 (c = 1, $CHCl_3$); the enantiomeric ratio (93:7 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 80:20, 1 mL/min, 28 °C, t_{Rmaj} = 10.1 min, t_{Rmin} = 17.0 min, 277 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, J = 8.2 Hz, 3H), 6.87 (d, J = 8.5 Hz, 2H), 6.62 (dd, J = 8.2, 2.3 Hz, 1H), 6.58 (d, J = 2.3 Hz, 1H), 4.48 (s, 1H), 4.07 (d, J = 7.6 Hz, 2H), 3.80 (s, 3H), 2.80 (dd, J = 13.8, 8.5 Hz, 1H), 2.61 (dd, J = 13.8, 7.2 Hz, 1H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.5, 158.2, 155.3, 151.7, 131.0, 130.9, 130.2, 122.1, 114.1, 110.3, 65.2, 64.6, 55.4, 40.1, 31.9, 21.2; HRMS(ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{20}O_5Na^+$ 351.1203, found 351.1208

*(1R,2S)-2-Benzyl-1,2,3,4-tetrahydronaphthalen-1-ol (cis-**5a**).* All spectra were in agreement with reported data.[68] Purified by PTLC (*n*-hexane/EtOAc 90:10) as a white solid (13 mg, 53% yield): $[\alpha]_D^{27}$ = +31.8 (c = 0.8, $CHCl_3$); the enantiomeric ratio (92:8 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 6.4 min, t_{Rmin} = 7.4 min, 208 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.11 (m, 9H), 4.56 (d, J = 3.0 Hz, 1H), 3.00 (dd, J = 13.5, 7.8 Hz, 1H), 2.93 (dd, J = 17.3, 5.4 Hz, 1H), 2.85−2.73 (m, 2H), 2.07 (dtd, J = 10.9, 7.5, 3.5 Hz, 1H), 1.88 (qd, J = 12.3, 5.6 Hz, 1H), 1.80−1.70 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.8, 138.6, 137.0, 130.2, 129.4, 129.3, 128.5, 128.1, 126.3, 126.0, 69.5, 41.9, 38.3, 29.3, 22.7. HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{18}ONa^+$ 261.1250, found 261.1263.

*(1R,2S)-2-(4-Chlorobenzyl)-1,2,3,4-tetrahydronaphthalen-1-ol (cis-**5b**).* This compound was only partially characterized.[69] Purified by PTLC (*n*-hexane/EtOAc 90:10) as an off-white solid (20 mg, 75% yield): $[\alpha]_D^{27}$ = +45.4 (c = 0.6, $CHCl_3$); the enantiomeric ratio (91:9 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 6.6 min, t_{Rmin}: 7.8 min, 208 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.10 (m, 8H), 4.47 (d, J = 3.1 Hz, 1H), 2.98−2.83 (m, 2H), 2.81−2.64 (m, 2H), 1.97 (dtd, J = 10.8, 7.6, 7.1, 3.5 Hz, 1H), 1.82 (qd, J = 12.4, 5.6 Hz, 1H), 1.75−1.64 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.3, 138.5, 136.9, 131.8, 130.7, 130.1, 129.3, 128.6, 128.3, 126.4, 69.3, 41.86, 37.7, 29.3, 22.7; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{17}ClONa^+$ 295.0860, found 295.0860.

*(1R,2S)-2-(4-Methoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-ol (cis-**5c**).* This compound was characterized only in a diastereoisomeric mixture (50:50).[70] Purified by PTLC (*n*-hexane/EtOAc 80:20) as a white solid (14 mg, 52% yield): $[\alpha]_D^{27}$ = +20.0 (c = 1, $CHCl_3$); the enantiomeric ratio (98:2 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 8.3 min, t_{Rmin} = 10.0 min, 278 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.07 (m, 6H), 6.86 (d, J = 8.5 Hz, 2H), 4.50 (d, J = 3.0 Hz, 1H), 3.80 (s, 3H), 2.94−2.82 (m, 2H), 2.79−2.61 (m, 2H), 2.05−1.91 (m, 1H), 1.81 (qd, J = 12.3, 5.6 Hz, 1H), 1.69 (ddd, J = 12.5, 6.1, 2.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.0, 138.7, 137.1, 132.8, 130.3, 130.2, 129.2, 128.1, 126.3, 113.8, 69.5, 55.5, 42.0, 37.4, 29.4, 22.7; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{20}O_2Na^+$ 291.1356, found 291.1355.

*(1R,2S)-2-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-ol (cis-**5d**).* Purified by PTLC (*n*-hexane/EtOAc 70:30) as a yellow oil (18 mg, 59% yield): $[\alpha]_D^{27}$ = +27.0 (c = 1, $CHCl_3$); the enantiomeric ratio (98:2 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 13.4 min, t_{Rmin} = 18.8 min, 278 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.06 (m, 4H), 6.87−6.72 (m, 3H), 4.52 (d, J = 3.0 Hz, 1H), 3.88 (s, 6H), 2.97−2.85 (m, 2H), 2.76 (ddd, J = 17.4, 11.7, 6.2 Hz, 1H), 2.68 (dd, J = 13.6, 7.3 Hz, 1H), 2.00 (dddd, J = 13.6, 10.7, 7.6, 3.0 Hz, 1H), 1.89−1.77 (m, 1H), 1.75−1.67 (m, 1H);

https://dx.doi.org/10.1021/acs.joc.0c02981
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$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.9, 147.3, 138.6, 137.1, 133.3, 130.2, 129.3, 128.2, 126.3, 121.2, 112.5, 111.3, 69.5, 56.1, 55.9, 41.9, 37.9, 29.4, 22.7; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{22}O_3Na^+$ 321.1461, found 321.1468.

*(1R,2S)-2-Benzyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (cis-**5e**).* Purified by PTLC (*n*-hexane/EtOAc 80:20) as a pale yellow oil (14 mg, 51% yield); the enantiomeric ratio (98:2 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 95:5, 1 mL/min, 28 °C, t_{Rmaj} = 15.4 min, t_{Rmin} = 16.5 min, 206 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.17 (m, 5H), 7.18−7.09 (m, 2H), 6.66 (dd, J = 8.4, 2.7 Hz, 1H), 6.56 (d, J = 2.6 Hz, 1H), 4.40 (d, J = 2.9 Hz, 1H), 3.70 (s, 3H), 2.87 (dd, J = 13.5, 7.8 Hz, 1H), 2.77 (ddd, J = 17.2, 5.8, 2.3 Hz, 1H), 2.71−2.59 (m, 2H), 1.92 (dddd, J = 10.5, 7.6, 4.6, 2.9 Hz, 1H), 1.74 (qd, J = 12.4, 5.7 Hz, 1H), 1.61 (ddd, J = 13.2, 5.9, 2.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.3, 140.9, 138.5, 131.3, 129.4, 128.5, 126.0, 113.5, 112.6, 69.1, 55.3, 42.1, 38.5, 29.8, 22.6; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{20}O_2Na^+$ 291.1356, found 291.1360.

*(1R,2S)-6-Methoxy-2-(4-methoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-ol (cis-**5f**).* Purified by PTLC (*n*-hexane/EtOAc 80:20) as a waxy yellow solid (14 mg, 48% yield): $[\alpha]_D^{27}$ = +28.3 (c = 0.5, $CHCl_3$); the enantiomeric ratio (97:3 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 13.0 min, t_{Rmin} = 19.3 min, 206 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.5 Hz, 3H), 6.86 (d, J = 8.6 Hz, 2H), 6.73 (dd, J = 8.5, 2.7 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 4.46 (d, J = 2.9 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.92−2.80 (m, 2H), 2.77−2.62 (m, 2H), 1.99−1.89 (m, 1H), 1.86−1.73 (m, 1H), 1.67 (ddt, J = 9.9, 6.3, 2.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.3, 157.9, 138.6, 132.8, 131.4, 131.3, 130.3, 113.9, 113.4, 112.6, 69.0, 55.4, 55.3, 42.2, 37.6, 29.8, 22.6; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{22}O_3Na^+$ 321.1461, found 321.1461.

*(1R,2S)-2-(3,4-Dimethoxybenzyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (cis-**5g**).* Purified by PTLC (*n*-hexane/EtOAc 70:30) as a yellow solid (15 mg, 44% yield): $[\alpha]_D^{27}$ = +22.8 (c = 1, $CHCl_3$); the enantiomeric ratio (>99:1 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 80:20, 1 mL/min, 28 °C, t_{Rmaj} = 11.1 min, t_{Rmin} = 27.7 min, 222 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 1H), 6.85−6.79 (m, 3H), 6.74 (dd, J = 8.5, 2.6 Hz, 1H), 6.64 (d, J = 2.6 Hz, 1H), 4.47 (d, J = 2.9 Hz, 1H), 3.88 (s, 6H), 3.77 (s, 3H), 2.92−2.82 (m, 2H), 2.74 (dt, J = 11.8, 6.0 Hz, 1H), 2.67 (dd, J = 13.6, 7.3 Hz, 1H), 1.96 (dtd, J = 13.4, 7.6, 7.2, 3.4 Hz, 1H), 1.81 (qd, J = 12.3, 5.7 Hz, 1H), 1.72−1.65 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.3, 148.9, 147.3, 138.5, 133.4, 131.4, 131.3, 121.2, 113.5, 112.6, 112.7, 111.2, 69.0, 56.1, 55.9, 55.4, 42.2, 38.1, 29.7, 22.6. HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{24}O_4Na^+$ 351.1567, found 351.1577.

*(1R,2S)-5,8-Dimethoxy-2-(4-methoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-ol (cis-**5h**).* Purified by PTLC (*n*-hexane/EtOAc 70:30) as a waxy yellow solid (14 mg, 42% yield): $[\alpha]_D^{27}$ = +66.3 (c = 1, $CHCl_3$); the enantiomeric ratio (99:1 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 15.4 min, t_{Rmin} = 19.2 min, 207 nm: ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.68 (q, J = 8.8 Hz, 2H), 4.83 (d, J = 3.3 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 2.98 (dd, J = 13.6, 7.3 Hz, 1H), 2.95−2.89 (m, 1H), 2.71 (dd, J = 13.8, 7.5 Hz, 1H), 2.38 (ddd, J = 18.1, 11.3, 6.8 Hz, 1H), 1.83 (qt, J = 8.7, 4.3 Hz, 1H), 1.78−1.66 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.8, 151.8, 151.5, 133.3, 130.3, 128.8, 127.7, 113.7, 108.9, 107.1, 63.7, 55.8, 55.6, 55.4, 41.4, 37.4, 24.3, 21.9; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{24}O_4Na^+$ 351.1567, found 351.1578.

Synthesis of (*cis*)-4a and (*cis*)-5c on a Larger Scale Catalyzed by 2 mol % (*R,R*)-1c. To a round-bottom flask were added the substrate **2a** or **3c** (1.0 mmol), RuCl[(*R,R*)-TsDPEN]-(mesitylene) **1c** (0.02 mmol, 12.4 mg), $Cu(OTf)_2$(0.04 mmol, 14.5 mg), CTAB (0.2 mmol, 72.9 mg), and dichloroethane (2 mL,) and the resulting mixture was stirred at rt for 15 min under an argon atmosphere. Then, a solution of sodium formate (5 mmol, 340 mg) in water (2 mL) was added, and the reaction mixture was stirred at room temperature for either 20 (**2a**) or 72 h (**3c**), diluted in AcOEt (60 mL), dried over Na_2SO_4, and filtered through a small pad of silica. The resulting crude was then purified by flash chromatography (in *n*-hexane/AcOEt), yielding the pure products (*R,R*)-**4a** (205.4 mg, 76% yield, 96:4 er) or (*R,S*)-**5c** (123.2 mg, 46% yield, 92:8 er).

General Procedure for the Synthesis of ketones 6 and 7.[46] To a solution of corresponding enantioenriched saturated alcohol *cis*-**4** or *cis*-**5** (0.05 mmol) in dichloromethane (2.5 mL, 0.02 M) at 0 °C was added Dess−Martin periodinane (DMP) (0.15 mmol, 3 equiv, 64 mg), and the mixture was stirred for 1 h at 0 °C. Then, the reaction was diluted in dichloromethane (15 mL) and washed with a 1:1 mixture of saturated solutions of $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by preparative thin layer chromatography (*n*-hexane/AcOEt), yielding the products **6** or **7** without significant losses of the enantiomeric excess.

*(S)-3-(4-Methoxybenzyl)chroman-4-one ((S)-**6a**).* All spectra were in agreement with reported data.[71] Purified by PTLC (*n*-hexane/EtOAc 90:10) as a white solid (9 mg, 70% yield): the enantiomeric ratio (95:5 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 0.5 mL/min, 28 °C, t_{Rmaj} = 16.8 min, t_{Rmin} = 16.2 min, 284 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.9, 1.7 Hz, 1H), 7.48 (ddd, J = 8.4, 7.1, 1.8 Hz, 1H), 7.16 (d, J = 8.6 Hz, 2H), 7.03 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 6.97 (dd, J = 8.4, 1.0 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 4.37 (dd, J = 11.5, 4.3 Hz, 1H), 4.18 (dd, J = 11.5, 8.1 Hz, 1H), 3.80 (s, 3H), 3.21 (dd, J = 14.1, 4.6 Hz, 1H), 2.88 (ddt, J = 10.3, 8.1, 4.4 Hz, 1H), 2.69 (dd, J = 14.1, 10.3 Hz, 1H). HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{16}O_3Na^+$ 291.0992, found 291.0994.

*(R)-3-(4-Methoxybenzyl)-7-(methoxymethoxy)chroman-4-one ((R)-**6c**).* Purified by PTLC (*n*-hexane/EtOAc 85:15) as a white solid (14 mg, 87% yield): the enantiomeric ratio (97:3 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 14.3 min, t_{Rmin} = 16.7 min, 268 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.69 (dd, J = 8.8, 2.3 Hz, 1H), 6.59 (d, J = 2.3 Hz, 1H), 5.20 (s, 2H), 4.34 (dd, J = 11.5, 4.2 Hz, 1H), 4.16 (dd, J = 11.4, 7.6 Hz, 1H), 3.80 (s, 3H), 3.48 (s, 3H), 3.19 (dd, J = 13.9, 4.4 Hz, 1H), 2.80 (ddt, J = 11.8, 8.2, 4.0 Hz, 1H), 2.67 (dd, J = 13.9, 10.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 192.90, 163.53, 163.40, 158.46, 130.39, 130.20, 129.34, 115.36, 114.15, 111.12, 103.45, 94.19, 69.78, 56.56, 55.36, 47.77, 31.90; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{20}O_5Na^+$ 351.1203, found 351.1203.

*(R)-2-(4-Methoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one ((R)-**7c**).* All spectra were in agreement with reported data;[72] Purified by PTLC (n-hexane/EtOAc 90:10) as a colorless oil (10 mg, 78% yield): $[\alpha]_D^{27}$ = +7.5 (c = 1, $CHCl_3$); the enantiomeric ratio (94:6 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 99:1, 0.5 mL/min, 28 °C, t_{Rmaj} = 24.0 min, t_{Rmin} = 25.5 min, 243 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 7.9, 1.4 Hz, 1H), 7.46 (td, J = 7.5, 1.4 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.7 Hz, 1H), 7.15 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.3 Hz, 2H), 3.80 (s, 3H), 3.40 (dd, J = 13.6, 3.9 Hz, 1H), 2.93 (dt, J = 9.5, 4.7 Hz, 2H), 2.70 (ddt, J = 10.9, 8.1, 4.1 Hz, 1H), 2.62 (dd, J = 13.6, 9.5 Hz, 1H), 2.11 (dt, J = 13.5, 4.5 Hz, 1H), 1.78 (ddt, J = 15.9, 10.8, 5.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 199.7, 158.1, 144.2, 133.4, 132.6, 132.1, 130.3, 128.81, 127.7, 126.8, 113.9, 55.4, 49.7, 34.9, 28.7, 27.7.; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{18}O_2Na^+$ 289.1199, found 289.1194.

*(S)-6-Methoxy-2-(4-methoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one ((S)-**7f**).* This compound was only partially described;[73] Purified by PTLC (*n*-hexane/EtOAc 85:15) as a waxy pale yellow solid (13 mg, 87% yield): $[\alpha]_D^{27}$ = −11.2 (c = 1, $CHCl_3$); the enantiomeric ratio (94:6 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 11.8 min, t_{Rmin} = 13.0 min, 269 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.6 Hz, 2H), 6.92−6.78 (m, 3H), 6.66 (d, J = 2.5 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.40 (dd, J = 13.1, 3.3 Hz, 1H), 2.99−2.81 (m, 2H), 2.72−2.55

https://dx.doi.org/10.1021/acs.joc.0c02981
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(m, 2H), 2.08 (dq, J = 13.6, 4.5 Hz, 1H), 1.83−1.70 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.5, 163.6, 158.1, 146.7, 132.3, 130.4, 130.2, 126.3, 113.9, 113.2, 112.6, 55.5, 55.3, 49.4, 35.0, 29.1, 27.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{21}O_3^+$ 297.1485, found 297.1486.

*(R)-7-Hydroxy-3-(4-methoxybenzyl)chroman-4-one ((R)-**10c**).*[49] To a solution of (*R*)-**6c** (0.05 mmol) in DCM (0,5 mL) were added $ZnBr_2$ (0.075 mmol, 17 mg) and *n*-BuSH (0.15 mmol, 16 μL). The reaction mixture was stirred at 0 °C for 1 h under an argon atmosphere. Then, the resulting mixture was diluted in DCM (10 mL) and filtered through a small pad of silica. The resulting crude was the purified by PTLC (*n*-hexane/AcOEt 70:30), yielding the pure product as a yellow solid (11 mg, 78% yield): $[\alpha]_D^{27}$ = −15.4 (c = 0.7, MeOH). All spectra were in agreement with reported data.[11] The enantiomeric ratio (92:8 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 20.1 min, t_{Rmin} = 22.7 min, 275 nm: ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.5 Hz, 1H), 7.14 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.52 (dd, J = 8.7, 2.3 Hz, 1H), 6.39 (d, J = 2.3 Hz, 1H), 4.35 (dd, J = 11.4, 4.2 Hz, 1H), 4.16 (dd, J = 11.4, 7.8 Hz, 1H), 3.80 (s, 3H), 3.20 (dd, J = 14.0, 4.4 Hz, 1H), 2.88−2.77 (m, 1H), 2.68 (dd, J = 13.9, 10.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 193.3, 163.8, 163.1, 158.4, 130.4, 130.2, 120.0, 114.6, 114.7, 110.8, 103.2, 69.7, 55.8, 47.7, 32.0; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{16}O_4Na^+$ 307.0941, found 307.0942.

*(E)-3-(4-Methoxybenzylidene)chroman-4-ol (rac-**8a**).*[74] Compound **2a** (0.2 mmol) was dissolved in methanol (2 mL), followed by the addition of $NaBH_4$ (0.6 mol, 3 equiv, 23 mg). The mixture was stirred for 1 h at rt, diluted in AcOEt (10 mL), and filtered through a small pad of silica. The resulting crude, a yellow solid (49 mg, 91% yield), was then used without further purification. All spectra were in agreement with reported data:[20] ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 7.7, 1.7 Hz, 1H), 7.26−7.11 (m, 3H), 6.96 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 7.2 Hz, 2H), 5.15 (s, 1H), 4.92 (q, J = 12.5 Hz, 2H), 3.81 (s, 3H); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{16}O_3Na^+$ 291.0992, found 291.0991.

*(S,E)-3-(4-Methoxybenzylidene)chroman-4-ol ((S)-**8a**).* All spectra were in agreement with reported data;[74] Isolated as the remaining starting material after the ATH of *rac*-**8a** under the conditions described in Scheme S2 . Purified by PTLC (*n*-hexane/EtOAc 80:20) as a yellow solid (7.5 mg, 28% yield): $[\alpha]_D^{27}$ = −29.6 (c = 0.75, $CHCl_3$); the enantiomeric ratio (99:1 er) was determined by HPLC analysis using a Chiralpack IA column, *n*-hexane/isopropyl alcohol 90:10, 1 mL/min, 28 °C, t_{Rmaj} = 18.6 min, t_{Rmin}: 17.5 min, 284 nm.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02981.

General information and procedures, HPLC analysis, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior−Brasil (CAPES), Finance Code 001, for the scholarships of G.S.C. and J.O.C.B. and the Programa de Cooperação Acadêmica−PROCAD for the scholarship of A.T.C. P.R.R.C. would like to thank the financial support of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; PQ-2017/311070/2017-5) and the Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ; CNE-FAPERJ E-26/203059/2016). We are grateful to Pontifícia Universidade Católica do Rio de Janeiro for NMR analyses and the Instituto de Química−UFRJ for NMR and optical rotation analyses. Universidade Federal do Rio do Janeiro, Universidade do Estado do Rio de Janeiro, and Instituto Militar de Engenharia are also acknowledged.

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