Enantioselective Synthesis of Chiral Oxygen-Containing Heterocycles Using Copper-Catalyzed Aryl C−O Coupling Reactions via Asymmetric Desymmetrization

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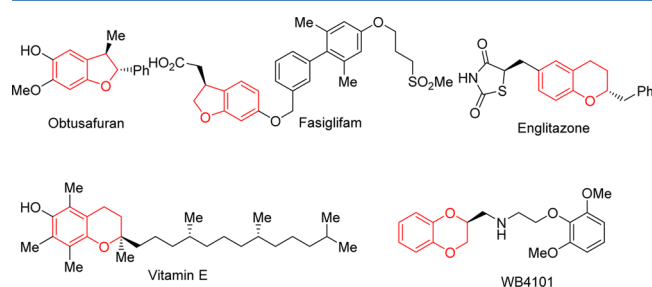[∥]College of Pharmacy, Linyi University, Shuangling Road, Linyi, 276000, China

Ⓢ *Supporting Information*

ABSTRACT: An enantioselective desymmetric aryl C−O coupling reaction was demonstrated under the catalysis of CuI and a chiral cyclic diamine ligand. A series of chiral oxygen-containing heterocyclic units such as 2,3-dihydrobenzofurans, chromans, and 1,4-benzodioxanes with tertiary or quaternary stereocarbon centers were synthesized with this method. DFT calculations were also carried out for a better understanding of the model for enantiocontrol.
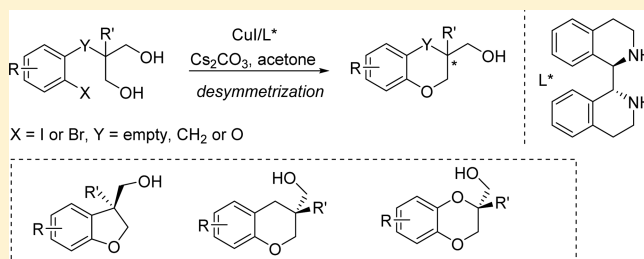
INTRODUCTION

Chiral oxygen-containing heterocyclic moieties such as 2,3-dihydrobenzofuran, chroman, and 1,4-benzodioxane are widely distributed in many bioactive natural products and pharmaceutical intermediates (Figure 1).[1−3] For examples, obtusafuran,[4] isolated from several *Dalbergia* species and featured with a dihydrobenzofuran structure, has the potent induction effect of the anticarcinogenic marker enzyme, quinone reductase; fasiglifam[5] and englitazone,[6] with dihydrobenzofuran and chroman structures respectively, are used as antidiabetic agetns; vitamine E,[7] with a key chroman ring bearing a quaternary stereochemical center, is an important intramembrane anti-oxidant; WB4101,[8] with a 1,4-benzodioxane key moiety, is a selective α_{1D}-adrenoceptor inhibitor.

Figure 1. Examples of bioactive natural products and pharmaceuticals containing dihydrobenzofuran, chroman, and 1,4-dioxane key structures.
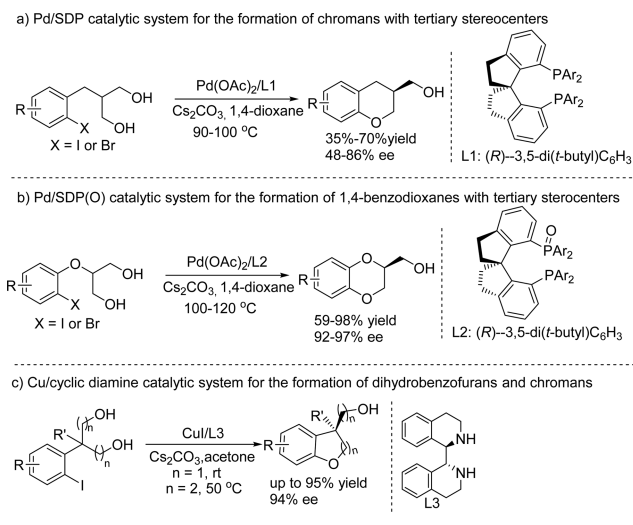
Due to the broad bioactivities of such oxygen-containing heterocycles, the asymmetric synthesis of chiral dihydrobenzo-furans, chromans, and 1,4-benzodioxanes has gained significant attention in recent decades.[2,9,10] In particular, a variety of elegant metal-catalyzed asymmetric transformations have been developed, such as an intramolecular Wacker-type cyclization,[11] allylic substitution,[12] allylic C−H oxidation,[13] and palladium-catalyzed asymmetric alkene aryloxyarylation.[14]

Asymmetric desymmetrization[15] is a general and powerful strategy for the enantioselective synthesis of chiral compounds. Great progress has been realized in this field in recent years.[16] Such a strategy has been extensively utilized in asymmetric reactions to differentiate two symmetric hydroxyl groups in a variety of 1,3-diols or analogues.[17] Our group[18] has focused on the asymmetric aryl carbon−heteroatom bond coupling through asymmetric desymmetrization or kinetic resolution.[19] In previous studies, we have developed two Pd-catalyzed systems for the enantioselective O-arylation via a desymmet-rization strategy (Scheme 1a, b): one is a Pd(OAc)$_2$/SDP (spirodiphosphine) catalytic system[20a] while the other is an improved Pd(OAc)$_2$/SDP(O) (spirodiphosphine monoxide) system.[20b] The former suffered from severe side reactions such as β-hydride elimination and dehalogenation during the formation of chromans. The latter could totally inhibit the dehalogenation and β-hydride elimination side reactions and greatly enhance the efficiency and enantioselectivity during the

Scheme 1. Previous Reports by Our Group in Asymmetric Desymmetric Aryl C–O Coupling Reactions for the Formation of Oxygen-Containing Chiral Heterocycles

a) Pd/SDP catalytic system for the formation of chromans with tertiary stereocenters

b) Pd/SDP(O) catalytic system for the formation of 1,4-benzodioxanes with tertiary sterocenters

c) Cu/cyclic diamine catalytic system for the formation of dihydrobenzofurans and chromans

Table 1. Asymmetric Desymmetrization of 2-(2-Bromoaryl)-1,3-diols for the Formation of Dihydrobenzofurans

2a: 87% yield, 88% ee

2b: 64% yield, 85% ee

2c: 74% yield, 85% ee

2d: 89% yield, 81% ee

2e: 88% yield, 78% ee

2f: 84% yield, 84.5% ee

2g: 76% yield, 78% ee

formation of 1,4-benzodioxane. However, both of these two catalytic systems were limited to a narrow class of substrates, and low efficiency and poor enantioselectivity were obtained for the enantioselective formation of the quaternary stereocarbon centers.

Recently, we have developed a Cu(I)/cyclic diamine (L3) catalytic system for intramolecular desymmetric O-aryaltion to assemble chiral dihydrobenzofurans and dihydrobenzopyrans bearing chiral centers adjacent to the aryl rings (Scheme 1c).[21] No dehalogenation or β-hydride elimination side reactions were observed in this catalytic system, and the coupling products were obtained in high yields and good to excellent ee values. More importantly, quaternary stereocenters in a variety of 3,3-disubstituted 2,3-dihydrobenzofurans were formed through this method in high yields and with good enantioselectivity. However, in these reactions, the majority of aryl halides investigated were aryl iodides, and only one example of aryl bromide was explored. Moreover, the enantioselective formation of quaternary stereocenters using the copper catalytic system has not been investigated in chromans and 1,4-benzodioxanes. Thus, to further explore the substrate scope of such a catalytic system, we studied the copper-catalyzed desymmetric reactions for the formation of chiral dihydrobenzofurans, dihydrobenzopyrans, and 1,4-benzodioxanes with a variety of aryl halides. Herein we wish to describe the details.

RESULTS AND DISCUSSION

Intramolecular Desymmetric O-Arylation of Aryl Bromides for the Formation of Dihydrobenzofurans. In a previous communication,[21] we explored one example of an aryl bromide for the formation of dihydrobenzofuran in which the yield and ee were slightly inferior to that of corresponding aryl iodide. Since aryl bromides are much cheaper than aryl iodides, we further explored other aryl bromides in such reactions. As shown in Table 1, a variety of aryl bromides were explored under the catalysis of CuI and L3 at 50 °C in acetone with Cs2CO3 as the base. The results are slightly inferior to that of corresponding aryl iodide substrates at room temperature. But high yields and good enantioselectivity were still obtained in all cases. The aryl chloride substrates were also tested in
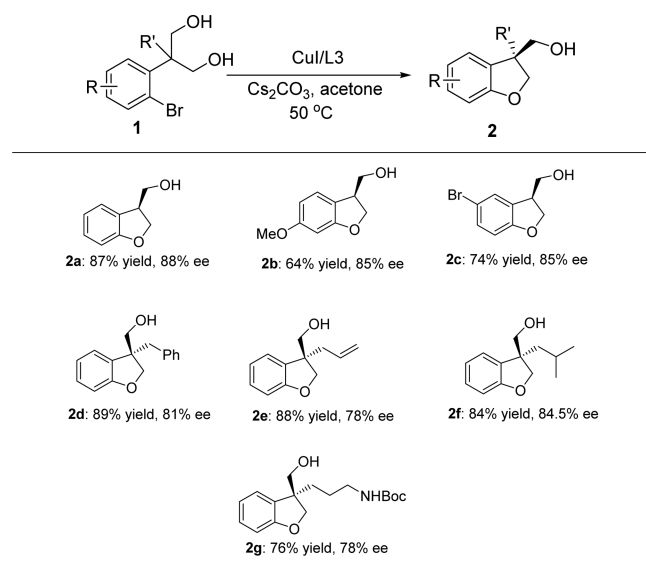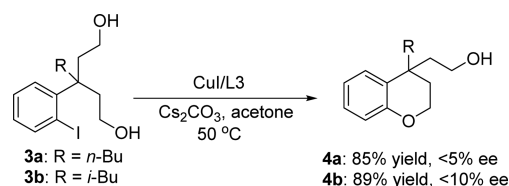
these reactions. However, no desired coupling products were obtained under the reaction conditions.

Intramolecular Desymmetric O-Arylation of Aryl Iodides for the Formation of Dihydrobenzopyrans Bearing Chiral Centers at 4-Position. In a previous communication,[21] we explored the asymmetric cyclization of a variety of 1,5-diols at 50 °C. The desired products, six-membered chromans bearing tertiary chiral carbon centers at the 4-positions, were delivered in high yields and excellent enantioselectivity. However, further exploration of the possibility for the enantioselective formation of chromans bearing quaternary chiral centers at the 4-position was unsuccessful. As shown in Scheme 2, although the cyclization of compounds **3a** and **3b** proceeded well and afforded the corresponding products **4a** and **4b** in excellent yields, the enantioselectivities were very poor.

Scheme 2. Asymmetric Desymmetrization of 1,5-Diols (3a/b) for the Formation of Quaternary Stereocenters

3a: R = n-Bu
3b: R = i-Bu

4a: 85% yield, <5% ee
4b: 89% yield, <10% ee

Intramolecular Desymmetric O-Arylation of Aryl Iodides for the Formation of Dihydrobenzopyrans Bearing Chiral Centers at the 3-Position. In our previous communication[21] via the copper catalyzed system, we did not explore the desymmetric coupling reaction for the formation of chromans bearing chiral carbon centers at the 3-position. In another previous communication[20a] with the Pd/SDP catalytic system, we explored such an idea and the coupling products were obtained in moderated yields and with moderate enantioselectivities. However, only those substrates with the potential to form tertiary chiral carbon centers could be used in the palladium catalytic system. Very poor enantioselectivity was obtained in an example for the asymmetric formation of

quaternary stereocenter in (3-methylchroman-3-yl)methanol (**6c**, 13% ee, data not shown). Thus, in this work, we explored the possibility to form chromans bearing chiral centers at the 3-position with the copper catalytic system.

As shown in Table 2, the desymmetric reactions of **5a** and **5b** were performed at room temperature and afforded the desired

Table 2. Asymmetric Desymmetrization of 1,3-Diols for the Formation of Chromans
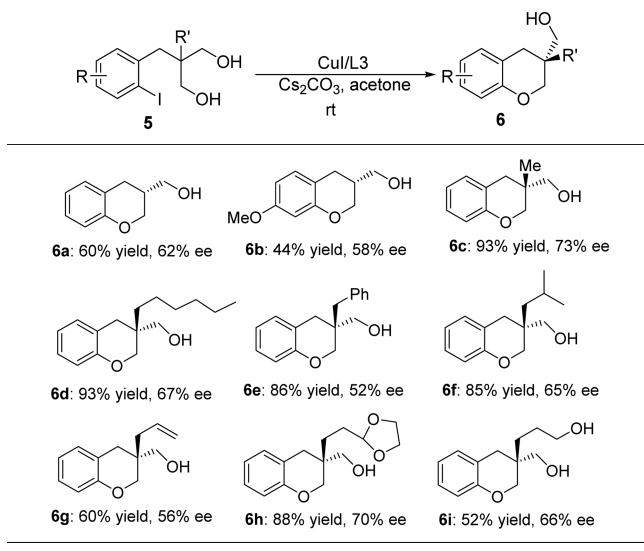
coupling products **6a** and **6b** in moderate yields and with moderate enantioselectivity. To our surprise, the reactions of other substrates (**5c–h**) with a substitution at the prochiral centers proceeded more smoothly than that of **5a,b**. The desired coupling products with quaternary stereocenters were furnished in high yields and moderate enantioselectivity. However, the reactions of corresponding aryl bromides were very slow even at an elevated temperature of 80 °C, and only trace amounts of desired coupling products were detected. The absolute configurations of **6a** and **6b** were assigned to be *R* by comparison with our previously reported data.[20a] The absolute configuration of **6c** was assigned to be *R* after simple transformation to compound **6c′** (Scheme 3), whose configuration was determined unambiguously by X-ray experiment.[22] The absolute configurations of **6d–h** were assigned by analogy to that of **6c**.

Intramolecular Desymmetric O-Arylation of Aryl Iodides for the Formation of 2-Hydroxymethyl-1,4-benzodioxanes. The asymmetric formation of 2-hydroxymethyl-1,4-benzodioxanes has also been explored in our previously reported palladium catalytic system, with SDP(O) as the chiral ligand.[20b] And similar to the case of the chromans

Scheme 3. Transformation of 6c and the Determination of Absolution Configuration
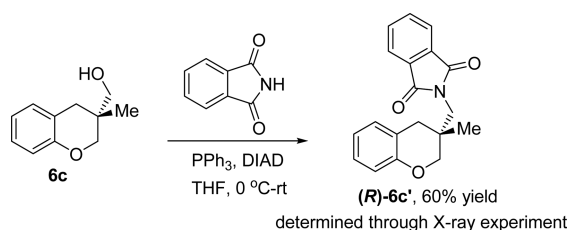
bearing chiral carbon centers at the 3-position, such reactions could only afford 2-hydroxymethyl-1,4-benzodioxanes with tertiary chiral centers. Thus, in this work, we retested this class of substrates with the copper catalytic system.

As shown in Table 3, the reaction of **7a** proceeded very slowly at 50 °C and afforded the coupling product **8a** in only

Table 3. Asymmetric Desymmetrization for the Formation of 1,4-Benzodioxanes
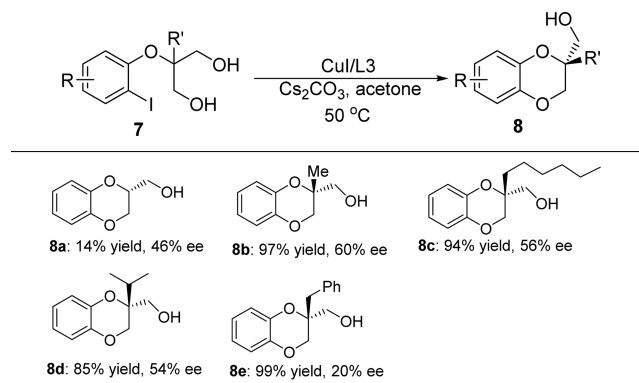
14% yield and with 46% ee. However, the substitutions at the prochiral centers greatly accelerated the reaction and furnished the desired coupling products with quaternary chiral centers in high yields and with moderate enantioselectivity (**8b–8d**). While in the case of **8e**, only 20% ee was obtained. Corresponding aryl bromide substrates proceeded very slowly at 50 °C or even an elevated temperature of 80 °C and afforded only a trace amount of the desired coupling products. Although the reason why the substitutions at the prochiral centers could accelerate the reactions is still unclear, we speculated that the increased steric hindrance may reduce the coordination effects of the substrates with the copper salt. The absolute configuration of **8a** was assigned as *R* by comparison with our previously reported data.[20b] The enantiopurity of **8b** was increased to more than 99% ee through simple recrystallization, and its absolute configuration was determined as *R* through X-ray experiment. The absolute configurations of **8c–e** were assigned by analogy to that of **8b**.

DFT Study of the Origin of Enantioselectivity. To understand the origin of enantioselectivity for different substrates, i.e. **1a** and **5a**, density functional theory (DFT) calculations were carried out (for computational details, see Supporting Information). The Cu-catalyzed cross-coupling reactions were generally considered to undergo a Cu^I/Cu^III catalytic cycle by an oxidative addition/reductive elimination pathway.[23] And the oxidative addition is commonly proposed to be the enantio-determining step.[24] The most stable transition structures leading to *R*- and *S*-configured products for both substrates **1a** and **5a** are depicted in Figure 2. The calculated preference is qualitative consistent with the experimental finding.

Diol forms 6-membered ring via a hydrogen bond, highlighted with yellow in Figure 2. This ring was found to be critical in determining the enantioselectivity. For the formation of dihydrobenzofurans from substrate **1a**, the hydrogen-bonding ring is perpendicular to the aryl group. In the *R*-transition state, there is a repulsive interaction between Br atom and the hydroxyl group which leads to the rotation of the −CH₂OH group to an unfavorable position. As shown in
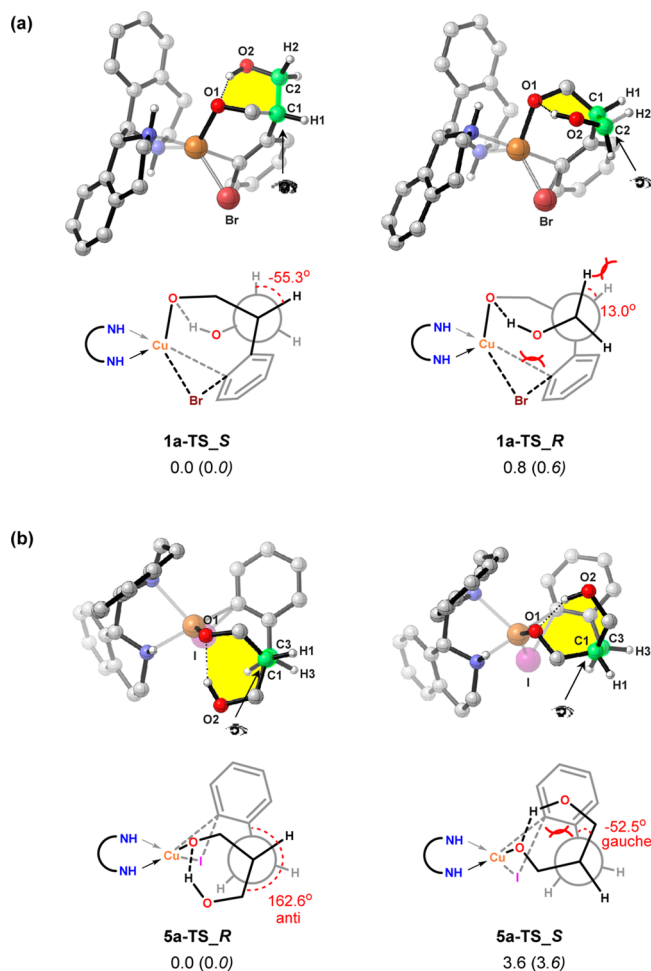
Figure 2. Optimized *S*- and *R*-configuration oxidative addition transition structures and their Newman projections along the highlighted (green) bond, (a) substrate **1a** and (b) substrate **5a**. Irrelevant hydrogen atoms are omitted for clarity. Relative free energies (*energies*) are in kcal/mol.

the Newman projection in Figure 2a, the dihedral angle θ, H1−C1−C2−H2, in **1a-TS_S** and **1a-TS_R** are −55.3° and 13.0°, indicating staggered and eclipsed conformations, respectively. Therefore, the S-product is more favorable.

For the formation of chromans from substrate **5a**, the additional CH$_2$ in the linker renders the hydrogen-bonding ring parallel with the aryl group. The coordination of the Cu center is similar to the **1a-TS**, except that the I atom turns toward the vertical position. The computed **5a-TS_R** is 3.6 kcal/mol more stable than **5a-TS_S**. In **5a-TS_R**, the −CH$_2$OH and aryl group are in an antiposition (dihedral angle θ, H1−C1−C3−H3, 162.6°). However, in **5a-TS_S**, the two groups present a gauche conformation (dihedral angle θ, H1−C1−C3−H3, −52.5°) resulting in a repulsive interaction between the aryl group and hydrogen-bonding ring.

CONCLUSION

Based on our previously reported CuI/cyclic diamine ligand (L3) catalytic system for the asymmetric desymmetric aryl C−O coupling reactions, the substrate scopes for the synthesis of chiral dihydrobenzofurans, chromans, and 1,4-benzodioxanes were widely investigated in this work. Although slightly inferior to those of aryl iodides, high yields and high enantioselectivity

were also obtained for the formation of chiral 2,3-dihydrobenzofurans bearing tertiary and quaternary stereocenters with the aryl bromide substrates. However, the current catalytic system seemed unsuccessful for the formation of quaternary stereocenters at the 4-position of chiral chromans and very poor enantioselectivity was observed in our examples. Moderate yields and moderate enantioselectivity were obtained in the formation of chiral chromans bearing tertiary and quaternary stereocenters at the 3-positions. Similar results were obtained in the cases of chiral 1,4-benzodioxanes with quaternary stereocenters. Although further optimization may be needed for better enantioselectivity, the current copper catalytic system provides an important complementary protocol to our previously reported palladium catalytic systems, especially for the formation of quaternary stereocenters in the oxygen-containing heterocycles. DFT calculations were also carried out for a better understanding of the model for enantiocontrol. Further exploration of this method is underway in our laboratory.

EXPERIMENTAL SECTION

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts (δ) are given relative to tetramethylsilane (δ 0.00 ppm) in CDCl$_3$. Coupling constants, J, were reported in hertz (Hz). High resolution mass spectra (HRMS) were obtained through the ESI/TOF-Q method. Enantiomeric ratios were determined by chiral HPLC analysis.

General Procedure for Copper-Catalyzed Coupling Reactions. The reaction mixture of aryl halides (0.3 mmol), L3 (0.045 mmol), CuI (0.03 mmol), and Cs$_2$CO$_3$ (0.6 mmol) in acetone (1.5 mL) was stirred at room temperature or an appointed temperature for 20 h. Then, H$_2$O (5.0 mL) and ethyl acetate (5.0 mL) were added into the mixture. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (5.0 mL × 3). The combined organic phase was washed with H$_2$O and brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/petroleum ether = 1/10 to 1/3) to afford the desired products. The chemical data for **2a−g**, **6a−b**, and **8a** were reported in our previous communications.[20]

2-(4-Butylchroman-4-yl)ethan-1-ol (4a). 60 mg, 85% yield, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.16−7.18 (m, 1H), 7.06−7.09 (m, 1H), 6.85−6.89 (m, 1H), 6.80 (d, J = 8.5 Hz, 1H), 4.17 (t, J = 5.5 Hz, 2H), 3.58−3.66 (m, 2H), 1.91−2.02 (m, 4H), 1.65−1.71 (m, 2H), 1.10−1.28 (m, 5H), 0.86 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.7, 128.6, 127.3, 127.2, 120.3, 117.2, 62.9, 59.5, 43.4, 41.6, 35.5, 31.8, 26.0, 23.3, 14.0; ESI-MS m/z 235.1 (M + H)$^+$; HRMS calcd for C$_{15}$H$_{23}$O$_2$$^+$ (M + H)$^+$ 235.1693, found 235.1688.

2-(4-Isobutylchroman-4-yl)ethan-1-ol (4b). 63 mg, 89% yield, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.18 (dd, J = 8.0, 1.0 Hz, 1H), 7.05−7.08 (m, 1H), 6.85−6.88 (m, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.15−4.18 (m, 2H), 3.56−3.64 (m, 2H), 1.94−2.04 (m, 4H), 1.56−1.74 (m, 3H), 1.30−1.34 (m, 1H), 0.90 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.8, 128.8, 127.4, 127.2, 120.3, 117.2, 63.1, 59.5, 50.5, 44.3, 36.2, 31.8, 25.5, 25.0, 24.2; ESI-MS m/z 235.1 (M + H)$^+$; HRMS calcd for C$_{15}$H$_{23}$O$_2$$^+$ (M + H)$^+$ 235.1693, found 235.1683.

(3-Methylchroman-3-yl)methanol (6c). 49.7 mg, 93% yield, white solid, melting point 75−77 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.09 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.86 (t, J = 7.6 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 4.04 (dd, J = 10.8, 1.2 Hz, 1H), 3.78 (d, J = 10.8 Hz, 1H), 3.57 (d, J = 10.8 Hz, 1H), 3.44 (d, J = 10.8 Hz, 1H), 2.67 (d, J = 16.4 Hz, 1H), 2.53 (d, J = 16.4 Hz, 1H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.9, 130.2, 127.2, 120.9, 120.7, 116.5, 71.5, 67.3, 63.4, 34.2, 33.8, 20.3; ESI-MS m/z 179.1 (M + H)$^+$; HRMS calcd for C$_{11}$H$_{15}$O$_2$$^+$ (M + H)$^+$ 179.1067, found 179.1059; HPLC Chiralpak

AS-H (hexane/*i*-PrOH = 97:3, 1.0 mL/min) τ_{major} = 19.3 min, τ_{minor} = 22.7 min. $[\alpha]_D^{25}$ −23.1 (*c* 1.0, CHCl$_3$, 73% ee).

(3-Hexylchroman-3-yl)methanol (6d). 69.5 mg, 93% yield, white solid, melting point 67−68 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.09 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 4.09 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.78 (d, *J* = 10.8 Hz, 1H), 3.57 (d, *J* = 10.8 Hz, 1H), 3.50 (d, *J* = 10.8 Hz, 1H), 2.63 (d, *J* = 16.4 Hz, 1H), 2.56 (d, *J* = 16.4 Hz, 1H), 1.45−1.49 (m, 1H), 1.26−1.32 (m, 9H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.2, 130.2, 127.1, 121.0, 120.7, 116.5, 70.7, 64.2, 36.2, 33.2, 32.5, 31.8, 30.1, 22.8, 22.6, 14.1; ESI-MS *m/z* 249.2 (M + H)$^+$; HRMS calcd for C$_{16}$H$_{25}$O$_2^+$ (M + H)$^+$ 249.1849, found 249.1849; HPLC Chiralpak AS-H (hexane/*i*-PrOH = 90:10, 1.0 mL/min) τ_{major} = 6.1 min, τ_{minor} = 15.0 min. $[\alpha]_D^{25}$ −21.0 (*c* 1.0, CHCl$_3$, 67% ee).

(3-Benzylchroman-3-yl)methanol (6e). 73 mg, 96% yield, white solid, melting point 77−78 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.18−7.32 (m, 5H), 7.07−7.11 (m, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.82−6.87 (m, 2H), 4.08 (dd, *J* = 10.8, 1.6 Hz, 1H), 3.85 (d, *J* = 10.8 Hz, 1H), 3.49 (d, *J* = 10.8 Hz, 1H), 3.40 (d, *J* = 10.8 Hz, 1H), 2.83 (d, *J* = 13.2 Hz, 1H), 2.67 (d, *J* = 16.4 Hz, 1H), 2.65 (d, *J* = 13.2 Hz, 1H), 2.49 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.0, 137.0, 130.6, 130.2, 128.3 127.3, 126.5, 120.8, 120.6, 116.5, 70.1, 63.9, 38.5, 37.4, 32.2; ESI-MS *m/z* 255.1 (M + H)$^+$; HRMS calcd for C$_{17}$H$_{19}$O$_2^+$ (M + H)$^+$ 255.1380, found 255.1365; HPLC Chiralpak AD-H (hexane/*i*-PrOH = 95:5, 1.0 mL/min) τ_{minor} = 14.0 min, τ_{major} = 15.3 min. $[\alpha]_D^{25}$ ∼0 (*c* 1.0, CHCl$_3$, 52% ee).

(3-Isobutylchroman-3-yl)methanol (6f). 56.4 mg, 85% yield, oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.08 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 4.09 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.75 (d, *J* = 11.0 Hz, 1H), 3.59 (d, *J* = 11.0 Hz, 1H), 3.51 (d, *J* = 11.0 Hz, 1H), 2.68 (d, *J* = 16.5 Hz, 1H), 2.58 (d, *J* = 16.5 Hz, 1H), 1.78−1.86 (m, 2H), 1.41 (dd, *J* = 14.5, 6.5 Hz, 1H), 1.24 (dd, *J* = 14.5, 6.5 Hz, 1H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.0, 129.1, 126.1, 120.0, 119.7, 115.4, 69.6, 63.3, 41.2, 35.8, 31.9, 24.3, 24.2, 22.5; ESI-MS *m/z* 221.1 (M + H)$^+$; HRMS calcd for C$_{14}$H$_{21}$O$_2^+$ (M + H)$^+$ 221.1536, found 221.1535; HPLC Chiralcel OD-H (hexane/*i*-PrOH = 95:5, 1.0 mL/min) τ_{major} = 8.8 min, τ_{minor} = 13.1 min. $[\alpha]_D^{25}$ −43.4 (*c* 1.5, CHCl$_3$, 65% ee).

(3-Allylchroman-3-yl)methanol (6g). 36.7 mg, 60% yield, oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.09 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.81−6.87 (m, 2H), 5.84−5.93 (m, 1H), 5.13−5.16 (m, 2H), 4.08 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.84 (d, *J* = 10.5 Hz, 1H), 3.57 (d, *J* = 11.0 Hz, 1H), 3.51 (d, *J* = 11.0 Hz, 1H), 2.65 (d, *J* = 16.5 Hz, 1H), 2.57 (d, *J* = 16.5 Hz, 1H), 2.28 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.13 (d, *J* = 13.5, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.1, 133.3, 130.2, 127.3, 120.8, 120.6, 118.7, 116.5, 70.3, 64.6, 37.6, 36.7, 32.1; ESI-MS *m/z* 227.1 (M + Na)$^+$; HRMS calcd for C$_{13}$H$_{16}$NaO$_2^+$ (M + Na)$^+$ 227.1043, found 227.1043; HPLC Chiralcel OD-H (hexane/*i*-PrOH = 95:5, 1.0 mL/min) τ_{major} = 10.6 min, τ_{minor} = 14.2 min. $[\alpha]_D^{25}$ −31.7 (*c* 0.4, CHCl$_3$, 56% ee).

3-(2-(1,3-Dioxolan-2-yl)ethyl)chroman-3-yl)methanol (6h). 69.7 mg, 88% yield, oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.09 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 4.87 (t, *J* = 4.8 Hz, 1H), 4.06 (d, *J* = 10.8 Hz, 1H), 3.93−3.99 (m, 2H), 3,84−3.87 (m, 2H), 3.80 (d, *J* = 10.8 Hz, 1H), 3.47−3.55 (m, 2H), 2.54−2.61 (m, 2H), 2.33 (brs, 1H), 1.60−1.64 (m, 2H), 1.43−1.48 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.2, 130.2, 127.2, 120.7, 120.6, 116.5, 104.6, 70.6, 65.0, 63.8, 36.0, 32.4, 27.1, 26.3; ESI-MS *m/z* 287.1 (M + H)$^+$; HRMS calcd for C$_{15}$H$_{20}$NaO$_4^+$ (M + Na)$^+$ 287.1254, found 287.1259; HPLC Chiralpak AD-H (hexane/*i*-PrOH = 90:10, 1.0 mL/min) τ_{minor} = 16.4 min, τ_{major} = 18.4 min. $[\alpha]_D^{25}$ −14.2 (*c* 1.2, CHCl$_3$, 70% ee).

3-(3-(Hydroxymethyl)chroman-3-yl)propan-1-ol (6i). 34.7 mg, 52% yield, white solid, melting point, 92−94 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.09 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 4.06 (d, *J* = 10.8 Hz, 1H), 3.81 (d, *J* = 10.8 Hz, 1H), 3,63−3.67 (m, 2H), 3.48−3.56 (m, 2H), 2.53−2.63 (m, 2H), 1.54−1.68 (m, 3H), 1.35−1.43 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.1, 130.2, 127.3, 120.8, 120.7, 116.5,

63.8, 63.1, 36.1, 32.6, 28.7, 25.7; ESI-MS *m/z* 223.1 (M + H)$^+$; HRMS calcd for C$_{13}$H$_{19}$O$_3^+$ (M + H)$^+$ 223.1329, found 223.1311; HPLC Chiralpak AD-H (hexane/*i*-PrOH = 90:10, 1.0 mL/min) τ_{major} = 12.8 min, τ_{minor} = 14.2 min. $[\alpha]_D^{25}$ −15.3 (*c* 0.9, CHCl$_3$, 66% ee).

(2-Methyl-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methanol (8b). 52.4 mg, 97% yield, white solid, melting point 85−86 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.81−6.91 (m, 4H), 4.16 (d, *J* = 11.2 Hz, 1H), 3.92 (d, *J* = 11.2 Hz, 1H), 3.72 (d, *J* = 12.0 Hz, 1H), 3.67 (d, *J* = 12.0 Hz, 1H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.4, 142.3, 121.9, 121.2, 117.5, 117.1, 74.9, 68.4, 65.4, 18.9; ESI-MS *m/z* 203.1 (M + Na)$^+$; HRMS calcd for C$_{10}$H$_{12}$NaO$_3^+$ (M + Na)$^+$ 203.0679, found 203.0689. HPLC Chiralpakcel AD-H (hexane/*i*-PrOH = 95:5, 1.0 mL/min), τ_{minor} = 10.3 min, τ_{major} = 11.0 min; $[\alpha]_D^{25}$ = −7.3 (*c* 0.9, CHCl$_3$, 60% ee).

(2-Hexyl-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methanol (8c). 70.5 mg, 94% yield, oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.82−6.90 (m, 4H), 4.16 (d, *J* = 11.6 Hz, 1H), 3.99 (d, *J* = 11.6 Hz, 1H), 3.75 (d, *J* = 12.0 Hz, 1H), 3.68 (d, *J* = 12.0 Hz, 1H), 1.62−1.76 (m, 2H), 1.37−1.40 (m, 2H), 1.20−1.34 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.7, 142.5, 121.9, 121.1, 117.5, 117.1, 76.8, 67.0, 63.4, 32.1, 31.7, 29.7, 22.9, 22.6, 14.0; ESI-MS *m/z* 273.1 (M + Na)$^+$; HRMS calcd for C$_{15}$H$_{22}$NaO$_3^+$ (M + Na)$^+$ 273.1461, found 273.1473. HPLC Chiralcel OD-H (hexane/*i*-PrOH = 95:5, 1.0 mL/min), τ_{minor} = 8.06 min, τ_{major} = 8.8 min; $[\alpha]_D^{25}$ = −6.5 (*c* 1.5, CHCl$_3$, 56% ee).

(2-Isopropyl-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methanol (8d). 53.1 mg, 85% yield, oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.81−6.91 (m, 4H), 4.20 (d, *J* = 11.6 Hz, 1H), 4.12 (d, *J* = 11.6 Hz, 1H), 3.83 (d, *J* = 12.0 Hz, 1H), 3.70 (d, *J* = 12.0 Hz, 1H), 2.26 (h, *J* = 7.2 Hz, 1H), 1.02 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.9, 142.7, 121.9, 121.0, 117.5, 117.0, 78.6, 65.2, 61.1, 29.5, 16.9, 16.3; ESI-MS *m/z* 231.1 (M + Na)$^+$; HRMS calcd for C$_{12}$H$_{16}$NaO$_3^+$ (M + Na)$^+$ 231.0992, found 231.1005. HPLC Chiralcel OD-H (hexane/*i*-PrOH = 95:5, 1.0 mL/min), τ_{major} = 9.5 min, τ_{minor} = 12.9 min; $[\alpha]_D^{25}$ = −7.5 (*c* 1.0, CHCl$_3$, 54% ee).

(2-Benzyl-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methanol (8e). 76.1 mg, 99% yield, oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22−7.32 (m, 5H), 6.84−6.94 (m, 4H), 4.06 (d, *J* = 11.6 Hz, 1H), 3.98 (d, *J* = 11.6 Hz, 1H), 3.68 (d, *J* = 12.0 Hz, 1H), 3.59 (d, *J* = 12.0 Hz, 1H), 3.08 (d, *J* = 14.0 Hz, 1H), 2.97 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.7, 142.2, 135.4, 130.5, 128.4, 126.9, 122.1, 121.3, 117.6, 117.2, 76.9, 66.5, 63.1; ESI-MS *m/z* 279.1 (M + Na)$^+$; HRMS calcd for C$_{16}$H$_{16}$NaO$_3^+$ (M + Na)$^+$ 279.0992, found 279.1003. HPLC Chiralpak AD-H (hexane/*i*-PrOH = 95:5, 1.0 mL/min), τ_{minor} = 12.7 min, τ_{major} = 13.9 min; $[\alpha]_D^{25}$ = −2.1 (*c* 1.5, CHCl$_3$, 20% ee).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02646.

> The X-ray experimental data, the computational details, ^{1}H and ^{13}C NMR, HPLC spectra (PDF)
> Crystallographic data (CIF, CIF)

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Notes

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