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

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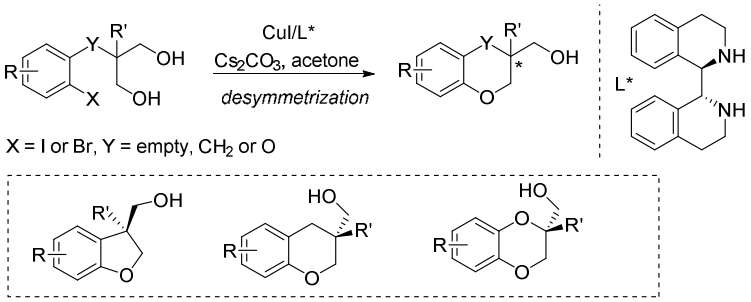
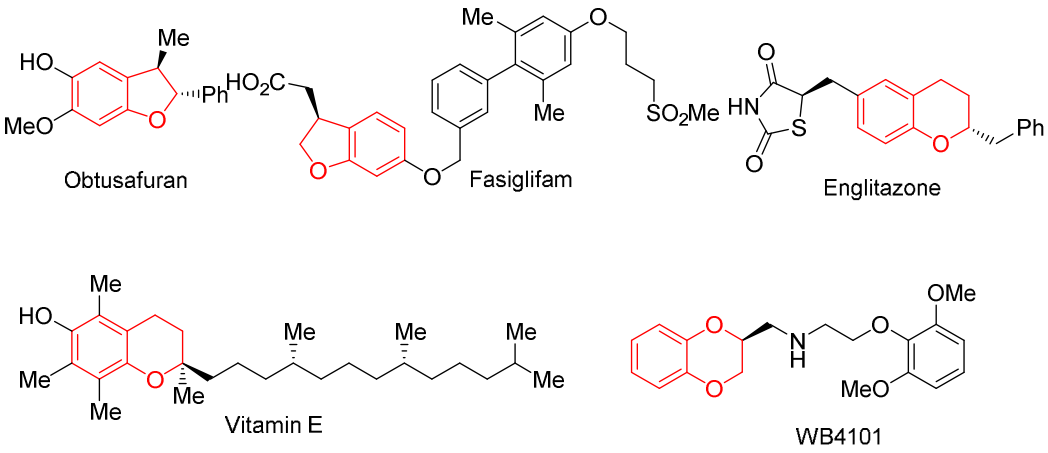


Abstract: *An enantioselective desymmetric aryl C-O coupling reaction was demonstrated under the catalysis of CuI and a chiral cyclic diamine ligand. A series of chiral oxygen-containing heterocyclic units such as 2,3-dihydrobenzofurans, chromans and 1,4-benzodioxanes with tertiary or quaternary stereocarbon centers were synthesized with this method. DFT calculations were also carried out for 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 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 antioxidant; WB-4101[8] with 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.



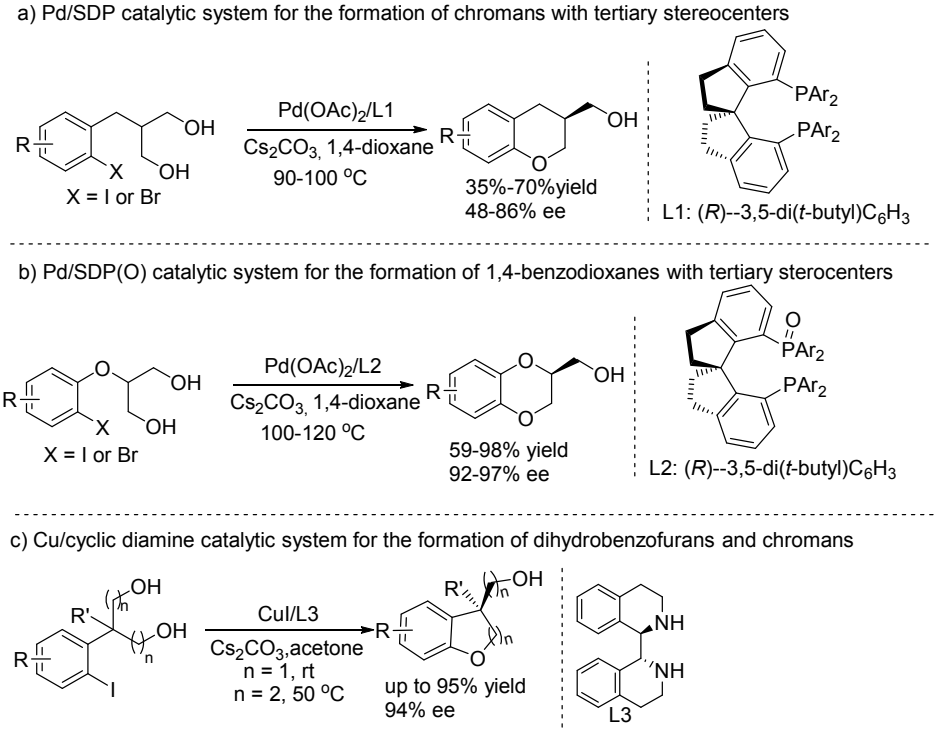
Due to the broad bioactivities of such oxygen-containing heterocycles, the asymmetric synthesis of chiral dihydrobenzofurans, chromans and 1,4-benzodioxanes has gained significant attentions over the past many years.[2,9-10] In particular, a variety of elegant metal-catalyzed asymmetric transformations 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 the previous studies, we have developed two Pd-catalyzed systems for the enantioselective O-arylation via a desymmetrization strategy (Scheme 1a/b): one is a $Pd(OAc)_2$/SDP (spirodiphosphine) catalytic system[20a] while the another 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 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. What's more, the enantioselective formation of quaternary stereocenters using the copper catalytic system hasn't 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.

Scheme 1. Previous reports by our group in asymmetric desymmetric aryl C-O coupling reactions for the formation of oxygen-containing chiral heterocycles.

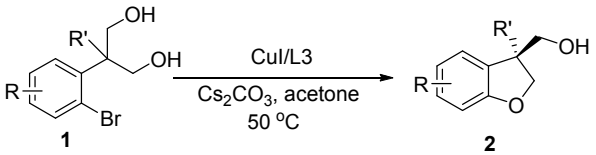


RESULTS AND DISCUSSION

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 Cs_2CO_3 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.

Table 1. Asymmetric desymmetrization of 2-(2-bromoaryl)-1,3-diols for the formation of dihydrobenzofurans.



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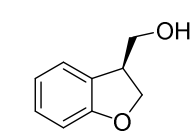
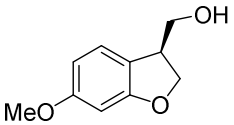
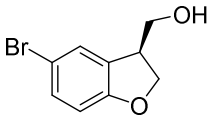


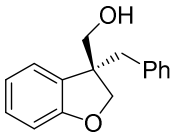
2a: 87% yield, 88% ee



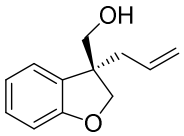
2b: 64% yield, 85% ee



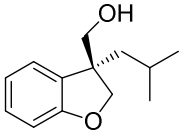
2c: 74% yield, 85% ee



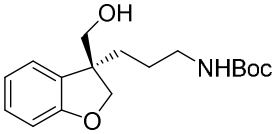
2d: 89% yield, 81% ee



2e: 88% yield, 78% ee



2f: 84% yield, 84.5% ee

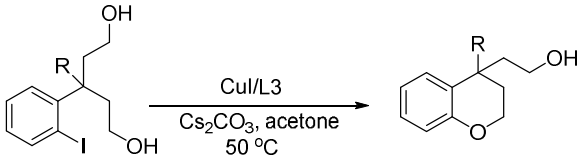


2g: 76% yield, 78% ee

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, 6-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.



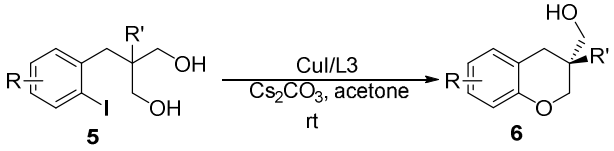
3a: R = *n*-Bu
3b: R = *i*-Bu

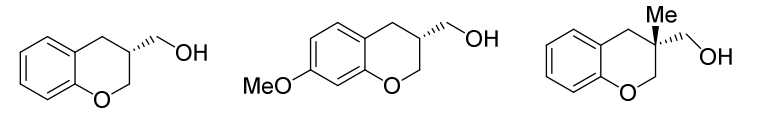
4a: 85% yield, <5% ee
4b: 89% yield, <10% ee

Intramolecular desymmetric O-arylation of aryl iodides for the formation of dihydrobenzopyrans bearing chiral centers at 3-position.

In our previous communication[21] via the copper catalyzed system, we didn't explore the desymmetric coupling reaction for the formation of chromans bearing chiral carbon centers at the 3-positions. 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 3-positions with the copper catalytic system.

Table 2. Asymmetric desymmetrization of 1,3-diols for the formation of chromans

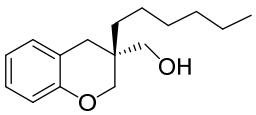




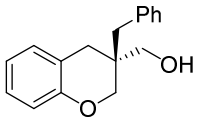
6a: 60% yield, 62% ee

6b: 44% yield, 58% ee

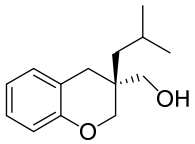
6c: 93% yield, 73% ee



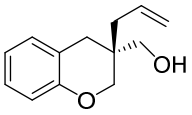
6d: 93% yield, 67% ee



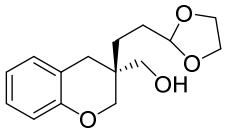
6e: 86% yield, 52% ee



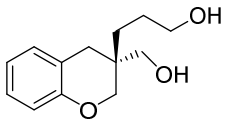
6f: 85% yield, 65% ee



6g: 60% yield, 56% ee



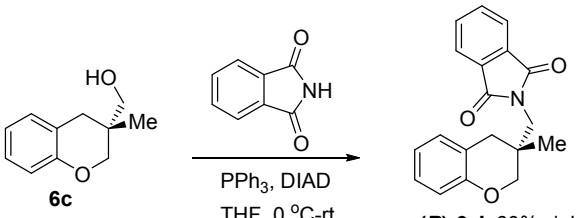
6h: 88% yield, 70% ee



6i: 52% yield, 66% ee

As shown in Table 2, the desymmetric reactions of **5a** and **5b** were performed at room temperature and afforded the desired 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 elevated temperature of 80 ^{o}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**.

Scheme 3. The transformation of **6c** and the determination of absolution configuration

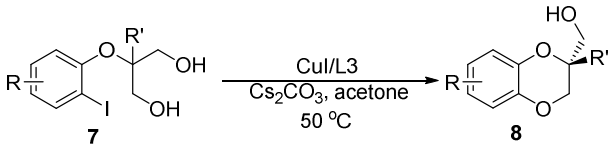


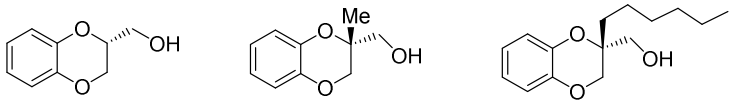
Intramolecular desymmetric O-arylation of aryl iodides for the formation of 2-hydroxymethyl-1,4-benzodioxanes.

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 that of the chromans bearing chiral carbon centers at the 3-positions, such reactions could only afford 2-hydroxymethyl-1,4-benzodioxanes with tertiary chiral centers. Thus, in this work, we re-tested 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 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 elevated temperature of 80 °C and afforded only 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 analogue to that of **8b**.

Table 3. Asymmetric desymmetrization for the formation of 1,4-benzodioxanes

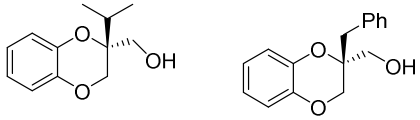




8a: 14% yield, 46% ee

8b: 97% yield, 60% ee

8c: 94% yield, 56% ee



8d: 85% yield, 54% ee

8e: 99% yield, 20% ee

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 (Computational details see SI). 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.

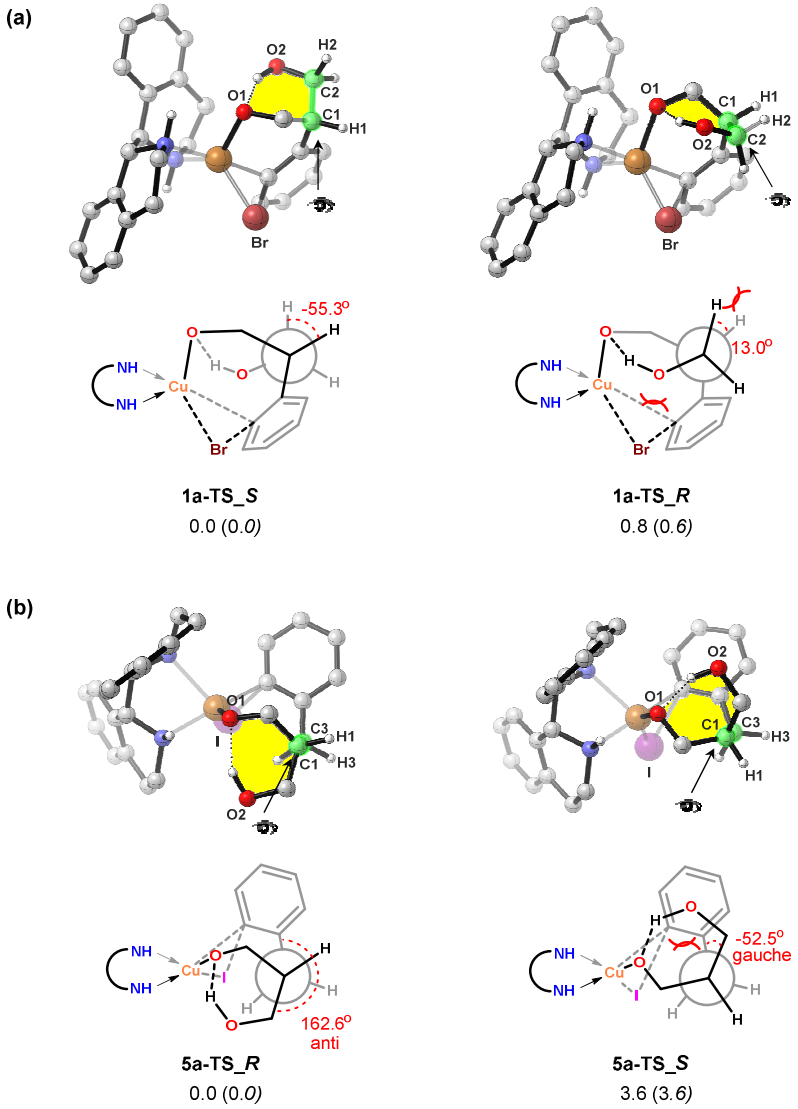


Figure 2. Optimized *S* and *R*-configuration oxidative addition transition structures and their Newman projections along the highlighted (green) bond, (a) substrate **1a** and (b) substrate **5a**. Irrelevant hydrogen atoms are omitted for clarity. Relative free energies (*energies*) are in kcal/mol.

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 $–CH_2OH$ group to an unfavorable position. As shown in the Newman projection in Figure 2(a), 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, 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 Cu center is similar to the **1a-TS**, except that the I atom turns to vertical position. The computed **5a-TS_*R*** is 3.6 kcal/mol more stable than **5a-TS_*S***. In **5a-TS_*R*,** the $–CH_2OH$ and aryl group are in an anti-position (dihedral angle θ, H1-C1-C3-H3, 162.6 ^{o}). However, in **5a-TS_*S***, the two groups present a gauche conformation (dihedral angle θ, H1-C1-C3-H3, -52.5 ^{o}) 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 a little inferior to that 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, 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, current copper catalytic system provides an important complimentary 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 better understanding of the model for enantiocontrol. Further exploration of this method is underway in our laboratory.

■ EXPERIMENTAL SECTION

General Remarks: ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts (δ) are given in relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$. Coupling constants, *J*, were reported in hertz unit (Hz). High resolution mass spectra (HRMS) were obtained through 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_2CO_3 (0.6 mmol) in acetone (1.5 mL) were stirred at room temperature or appointed temperature for 20 hours. Then H_2O (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_2O and brine, and dried over Na_2SO_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 of **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 ^{o}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. (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): 69.5mg, 93% yield, white solid, melting point 67-68 ^{o}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): 73mg, 96% yield, white solid, melting point 77-78 ^{o}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* = 7.5Hz, 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, CDCl3) 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; $[\alpha]^{25}{}_D$ = -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; $[\alpha]^{25}{}_D$ = -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; $[\alpha]^{25}_D$ = -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; $[\alpha]^{25}_D$ = -2.1 (c 1.5, $CHCl_3$, 20%ee).

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■ SUPPORTING INFORMATION

The X-ray experimental data, the computational details, ^{1}H and ^{13}C NMR, HPLC spectra.

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