INTRODUCTION

Chiral polyheterocyclic structures, especially those containing potential pharmacophores with multiple stereocenters, have attracted the continuous attention of the synthetic community owing to their wide range of biological properties. Despite extensive efforts, the development of novel synthetic strategies for the catalytic asymmetric synthesis of polyheterocyclic compounds from the readily available starting materials is still appealing but poses synthetic challenges, which may be attributed to the formation of multiple stereocenters in a completely stereocontrolled manner.

The enantioselective organocatalytic cascade reactions have been considered as powerful synthetic tools that enable the use of readily accessible starting materials to construct complex targets, particularly polyheterocyclic compounds with multiple stereocenters. Electron-deficient 1-aza-1,3-butadienes are versatile synthetic building blocks that allow for a wide range of cascade reactions to prepare nitrogen-containing chiral polycyclic compounds. Among the reported examples (Scheme 1), 1-aza-1,3-butadienes are commonly used as a four-atom unit for [4 + 2] annulations, such as the inverse-electron-demandaza-Diels−Alder reaction, to construct hydro pyridine derivatives, whereas the applications of 1-aza-1,3-butadienes as a two-carbon unit for [4 + 2] annulations has been much less developed.

We recently found that chroman-2-ol could be directly used in the asymmetric enamine catalysis to access chiral polyheterocyclic compounds bearing a chromane fragment, which is the main core of a wide variety of biologically active compounds. Although 2-hydroxy cinnamaldehyde could serve as the valuable precursor of chroman-2-ol under iminium-catalyzed reduction conditions, this feature opens the possibility of discovering the new application of 2-hydroxy cinnamaldehyde for the preparation of structurally diverse polyheterocyclic molecules via sequential cascade procedures. Indeed, there are other two reported examples of iminium-catalyzed enantioselective oxa-Michael-initiated cascade reactions, where the 2-hydroxy cinnamaldehyde was used to react with electron-deficient olefins, such as nitroolefins and methyleneindolinolines, for the preparation of polysubstituted chromane derivatives with good results. However, despite the wide applicability of 1-aza-1,3-butadienes in the sequential cascade synthesis of chiral polycyclic compounds, to the best of our knowledge, there is no report of asymmetric synthesis of highly functionalized chromane derivatives via [4 + 2] cycloaddition of 2-hydroxy cinnamaldehydes with 1-aza-1,3-butadienes as a two-carbon unit, leading to the products with the remaining ketimine moiety of 1-aza-1,3-butadienes, which offers ample opportunity for further transformations to provide diversified polyheterocyclic frameworks with high molecular and stereogenic complexity.

As a continuation of our ongoing investigation on the application of hemiacetals in organocatalytic asymmetric reactions to construct chiral polyheterocyclic structures, we...
became interested in designing a novel and reliable organocatalytic strategy, which could impart precise assignment of the roles between the reaction components, for the direct assembly of skeletally diverse chromane-containing polyheterocyclic compounds. In this work, we envisioned that the reaction of 1-aza-1,3-butadienes 1 and 2-hydroxy cinnamaldehyde 2a would proceed via two different reaction pathways, and the application of Hantzsch ester 4 is proposed to be the key to achieve role switch of both 2-hydroxy cinnamaldehydes and 1-aza-1,3-butadienes (Scheme 2). In path a, the corresponding chroman-2-ol is formed first by the iminium-catalyzed in situ reduction of 2-hydroxy cinnamaldehyde 2a in the presence of Hantzsch ester 4 as the organic hydride source, which can subsequently undergo enamine-catalyzed [4 + 2] cycloaddition (or inverse-electron-demandaza-Diels–Alder reaction) to give hemiaminal intermediate 5 with the use of 1-aza-1,3-butadiene as a four-atom unit. The subsequent acid-catalyzed iminium ion formation of hemiaminal intermediate 5 provided the desired polycyclic aminal-containing product 6a that contains three continuous stereogenic centers and an aminal moiety in good yield with excellent enantioselectivity as a single diastereoisomer (entry 1). It should be noted that the whole sequential cascade process was completed in a one-pot manner and only traces of competitive oxo-Michael initiated side product 7a (<5%) were detected, which indicated the high efficiency of this novel catalytic strategy. The use of other acidic additives resulted in slightly lower yields but with similar good enantioselectivities (entries 2–4). No reaction was observed with basic additive NaOAc (entry 5). After further examination of different solvents (entries 6–10), acetone was determined to be the most effective solvent with regard to the yield, enantioselectivity, and reaction times of both steps. The catalyst loading could be reduced to 10 mol % without compromising the efficiency and enantioselectivity (entry 11).

Having established the optimal reaction conditions for the application of 1-aza-1,3-butadiene 1a as a four-atom unit in the...
reaction with 2-hydroxy cinnamaldehyde 2a via a one-pot cascade process, the substrate scope for the preparation of polycyclic aminal-containing chromane derivatives 6 was then investigated with regard to 1 and 2. As shown in Scheme 3, the reaction tolerates different substituted phenyl groups in the β-position of 1 (6a−d). Moreover, 2-naphthyl- and 2-thienyl-substituted 1 were effective substrates, affording 6e and 6f with excellent enantio- and diastereoselectivities. The functionalized 2b and 2c were also found to be applicable to this reaction sequence (6g and 6h). In addition, the analogous 1-azadiene 1′ containing 1,2,3-benzoxathiazine-2,2-dioxide motif was effectively applied in the reaction with 2a under the same reaction conditions, leading to 6h in good yield and stereocontrol.

Inspired by the successful implementation of 1-aza-1,3-butadienes 1 as a four-atom unit to synthesize polycyclic aminal-containing chromane derivatives 6 by the reaction with 2-hydroxy cinnamaldehydes 2 in the presence of Hantzsch ester 4, we further attempted to explore the use of 1-aza-1,3-butadienes 1 as a two-carbon unit in the reaction with 2-hydroxy cinnamaldehydes 2 in the absence of Hantzsch ester 4 to provide chromane-containing polycyclic products with more structural diversity. As shown in Table 2, a screening of a model reaction between 1a and 2a was initiated in the absence of Hantzsch ester 4 to access the switched reaction pathway. However, to our surprise, under the optimized conditions for the synthesis of 6, the oxa-Michael-initiated cascade reaction between 1a and 2a did not take place at all (entry 1). Interestingly, with benzoic acid (whose acidity is weaker than p-NBA) instead of p-NBA, the corresponding product 7a was obtained in 40% yield with high enantioselectivity (entry 2). This suggests that basic additives may be beneficial to the reactivity. As expected, the basic additives, such as NaOAc and N,N-diisopropylethylamine (DIPEA), increased the rate of the cascade reaction (entries 3 and 4), which can be explained by a possible deprotonative activation of the 2-hydroxy cinnamaldehyde 2a to form a more reactive intermediate with catalyst 3a. Not surprisingly, the cascade reaction proceeded smoothly with only aminocatalyst 3a and neither acidic nor basic additive was necessary (entry 5). On the other hand, after a brief screening of the solvent, the use of chlorinated solvent (1,2-dichloroethane, DCE) was found to be beneficial to the reaction rate (entry 6), whereas maintaining the enantioselectivity and all other solvents, such as MeCN, tetrahydrofuran

Table 1. Optimization Studies for Path a<sup>ab</sup>

| entry | additive | solvent | step 1 | step 2 | yield (%)<sup>b</sup> | ee (%)<sup>c</sup> |
|-------|----------|---------|--------|--------|-----------------------|------------------|
| 1     | p-NBA    | CHCl₃   | 24     | 2      | 65                    | 98               |
| 2     | BA       | CHCl₃   | 24     | 2      | 59                    | 94               |
| 3     | o-FBA    | CHCl₃   | 24     | 2      | 56                    | 95               |
| 4     | AcOH     | CHCl₃   | 24     | 2      | 51                    | 95               |
| 5     | NaOAc    | CHCl₃   | >48    | 2      |                       |                  |
| 6     | p-NBA    | toluene | 30     | 2      | 48                    | 99               |
| 7     | p-NBA    | THF     | 27     | >12    | 61                    | 91               |
| 8     | p-NBA    | acetone | 8      | 6      | 65                    | 97               |
| 9     | p-NBA    | MeCN    | 20     | 2      | 54                    | 91               |
| 10    | p-NBA    | MeOH    | 15     | 12     | 25                    | 89               |
| 11    | p-NBA    | acetone | 12     | 6      | 70                    | 97               |

<sup>a</sup>Unless otherwise noted, all reactions were carried out using 1a (0.10 mmol, 1.0 equiv), 2a (0.12 mmol, 1.2 equiv), 4 (0.12 mmol, 1.2 equiv) in solvent (0.2 mL) with 3a (20 mol %) and additives (20 mol %) at 40 °C. After 1a was consumed, p-TsOH (3.5 equiv) was added and then the reaction mixture was stirred at 25 °C for a specified time. <sup>b</sup>Isolated yield of 6a. Determined by high-performance liquid chromatography (HPLC) analysis on chiral stationary phases. <sup>c</sup>Reaction was carried out with 3a (10 mol %) and p-NBA (20 mol %) in 0.1 mL acetone.
THF, and acetone, resulted in sluggish reactions (entries 7–9), leading to very poor conversions even after 96 h. Finally, catalyst screening revealed that tert-butyldimethylsilyl (TBS)-protected diphenylprolinol catalyst 3b proved to be an effective catalyst without additives (entries 10 and 11), providing highly functionalized chromane product 7a in 71% yield with excellent stereoselectivity (97% enantiomeric excess (ee), diastereomeric ratio > 20:1). Therefore, with regard to enantioselectivity, the optimal conditions for the enantioselective preparation of 7a were found to be the use of 3b as a catalyst in DCE at 25 °C.

Subsequently, the substrate scope for the one-pot cascade sequence was explored. As shown in Scheme 4, highly stereoselective reactions proceeded using an array of 1-aza-1,3-butadienes 1 with electron-withdrawing or electron-donating substituents on the aromatic ring at different positions (7a–d). Excellent enantioselectivities were also gained for 2-naphthyl-substituted 1 (7e). 2-Hydroxy cinnamaldehyde 2b bearing a fluoro substituent on the aryl ring provided the desired product 7f in a good yield and with excellent stereoselectivity. Additionally, the analogous 1-azadiene 1' containing the 1,2,3-benzoxathiazine-2,2-dioxide motif was effectively applied in the cascade reaction process, leading to 7g in good yield and stereocontrol.

To explore the utility of this synthetic method, a larger-scale synthesis of product 7a was performed under the standard conditions (Scheme 5). To our delight, this larger-scale reaction (0.5 mmol) proceeded smoothly to provide chromane product 7a containing an aldehyde group and a ketimine moiety. As mentioned above, the remaining ketimine moiety in the structure of 7a could be potentially used for further transformations. The in situ Wittig reaction of 7a and ylide 8 generated enone 9, followed by the formation of an aminal fragment by the nucleophilic attack of MeOH to the ketimine moiety, which facilitated a subsequent intramolecularaza-Michael addition to give polyheterocyclic product 10 in good isolated yield (40% over three steps) and with high structural and stereogenic complexity. It should be noted that product 10 was obtained as a single diastereoisomer bearing five stereocenters and one is a tetrasubstituted stereogenic center.

The absolute configuration of product 6a (CCDC 1873976) and 10 (CCDC 1873974) was unequivocally determined by X-ray crystallographic analysis (see Scheme 3 for 6a and Scheme 5 for 10; the H atoms are omitted for clarity) and all other products were assigned by analogy.

**CONCLUSIONS**

In summary, we have developed two asymmetric organocatalytic competitive cascade reaction pathways: (1) 1-aza-1,3-
butadienes were used as a four-atom unit to react with 2-hydroxy cinnamaldehydes via a one-pot \([4 + 2]\) cycloaddition/iminium ion induced aminal formation cascade sequence and (2) 1-aza-1,3-butadienes were used as a two-carbon unit to

Table 2. Optimization Studies for Path b<sup>abcd</sup>

| entry | 3   | additive | solvent | T (h) | yield (%)<sup>b</sup> | ee (%)<sup>c</sup> |
|-------|-----|----------|---------|-------|------------------------|------------------|
| 1     | 3a  | p-NBA    | CHCl₃   | >96   |                        |                  |
| 2     | 3a  | BA       | CHCl₃   | 12    | 40                     | 94               |
| 3     | 3a  | NaOAc    | CHCl₃   | 12    | 71                     | 95               |
| 4     | 3a  | DIPEA    | CHCl₃   | 24    | 60                     | 91               |
| 5     | 3a  | MeCN     | CHCl₃   | 12    | 62                     | 93               |
| 6     | 3a  | THF      | CHCl₃   | >96   |                        |                  |
| 7     | 3a  | acetone  | CHCl₃   | >96   |                        |                  |
| 8     | 3a  | DCE      | CHCl₃   | 12    | 71                     | 93               |
| 9     | 3a  | DCE      | CHCl₃   | 24    | 71                     | 97               |
| 10    | 3b  | DCE      | CHCl₃   | 24    | 67                     | 80               |
| 11    | 3c  | DCE      | CHCl₃   | 24    | 67                     | 80               |

<sup>a</sup>Unless otherwise specified, all reactions were carried out using 2a (0.10 mmol, 1.0 equiv), 1a (0.12 mmol, 1.2 equiv) in solvent (600 μL) with catalyst 3 (20 mol %) and additives (20 mol %) at 25 °C for a specified time. Isolated yield of 7a. Determined by chiral HPLC analysis on the products after the in situ Wittig reaction with Ph₃P=CHCOPh; see the Supporting Information for more details. <sup>d</sup>TBS = tert-butyldimethylsilyl; TES = triethylsilyl.

Scheme 4. Substrate Scope of Path b
react with 2-hydroxy cinnamaldehydes via an oxa-Michael/Michael cascade sequence. The application of Hantzsch ester is proposed to be the key to achieve the switch between these two different cascade reaction pathways, providing poly cyclic chromane-containing compounds with high structural and stereogenic complexity. Finally, the designed cascade sequence is amenable to a larger scale, with a negligible di stereogenic complexity. General Procedure for the Asymmetric Synthesis of Polycyclic Chromane-Containing Products 6. A glass vial equipped with a magnetic stirring bar was charged with 2 (0.12 mmol, 1.2 equiv), 3a (3.2 mg, 0.01 mmol), and p-NO₂C₆H₄COOH (3.4 mg, 0.02 mmol) in acetone (0.1 mL) at 40 °C and then Hantzsch ester 4 (30 mg, 0.12 mmol) and 1 (0.10 mmol, 1.0 equiv) were added simultaneously. Reactions were carried out at 40 °C. After 1 was consumed, p-TsOH (60 mg, 0.35 mmol) and additional acetone (0.1 mL) were added, and the reaction mixture was then stirred at 25 °C for another 6 h. After the reaction was completed, the product was purified by column chromatography on silica gel using petroleum ether–ethyl acetate solvent mixture as the eluent to provide the desired poly cyclic chromane-containing products 6.

General Methods. 1H and 13C NMR spectra were recorded by an Agilent DD2-500 MHz NMR spectrometer, and the chemical shifts (δ) for 1H and 13C are given in parts per million (ppm) relative to residual signals of the solvent (CDCl₃ at 7.26 ppm 1H NMR and 77.16 ppm 13C NMR). The chemical shifts (δ) for some residual solvents in CDCl₃ are labeled in the spectra (H₂O at 1.56 ppm 1H NMR, CH₂Cl₂ at 5.30 ppm 1H NMR, ethyl acetate at 4.12, 2.05, 1.06 ppm 1H NMR, and diethyl ether at 3.48, 1.21 ppm 1H NMR, grease (CDCl₃ at 7.26 ppm 1H NMR and 77.16 ppm 13C NMR). The multiplicity: s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. High-resolution mass spectra (HRMS) are obtained with the Waters Q-Tof Ultima Global. X-ray data are analyzed from the Zhongke Chemical Technology Service Center. Optical rotations are reported as follows: [α]_{D}^{20} (c in g per 100 mL, solvent). All reactions are carried out at the bench with commercial reagents and solvent without further purification. Chiral HPLC analysis is performed on a HITACHI Chromaster. Daicel Chiralpak IA, IB, and IC columns with i-PrOH/n-hexane/CH₂Cl₂ as the eluent are used. HPLC traces were compared to racemic samples prepared by a mixture of two enantiomeric final products obtained using (S) and (R) catalysts.

Materials. Commercial reagents and solvents from Sigma-Aldrich, Fluka, Adamas, Aladdin, J&K, Meryer, Energy, and Alfa Aesar are used as-received without further purification. The catalysts (S)- and (R)-diphenylprolinol silyl ether are commercially available from Daicel Chiral Technologies. All of the 2-hydroxy cinnamaldehydes 2 are synthesized from the corresponding salicylaldehydes via the Wittig reaction. The substituted cyclic 1-azadienes 1 were prepared from 3-methylbenzo[d]isothiazole 1,1-dioxide and the corresponding aldehyde.
by HPLC analysis on Daichel Chiralpak IA column (n-hexane/i-
PrOH = 80:20, 1 mL/min), λ = 225 nm, τmajor = 12.60 min, τminor = 19.83 min, ee = 99%.

(656α,6α,12αR)-6-[(4-Chlorophenyl)-6α,12α-dihydro-6H,7-H
benzo[4,5]isothiazolo[2,3-α]chromeno[3,2-e]pyridine 14,14-
Dioxide (6c). White solid (24 mg, 56%); 1H NMR (500 MHz,
CDCl3) δ 7.88 (d, J = 7.8 Hz, 1H), 7.69–7.64 (m, 2H), 7.64–
7.57 (m, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.17 (t, J = 7.7 Hz,
1H), 7.10 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 7.4 Hz, 1H), 6.98–
6.90 (m, 2H), 6.03 (d, J = 2.1 Hz, 1H), 5.67 (d, J = 2.6 Hz,
1H), 3.58 (dd, J = 10.5, 2.5 Hz, 1H), 3.07 (dd, J = 17.0, 5.9
Hz, 1H), 2.62 (dd, J = 17.1, 2.4 Hz, 1H), 2.48–2.37 (m, 1H).
13C NMR (125 MHz, CDCl3) δ 151.5, 140.5, 133.3, 133.2,
132.4, 130.4, 129.8, 129.3, 129.1, 128.8, 128.8, 128.2, 121.8,
121.4, 121.3, 118.3, 117.5, 103.4, 76.4, 38.7, 37.4, 27.6. ESI-
HRMS: [M + H]+ calcld. For C22H18NO3S2 m/z: 436.0769; found: 436.0764. (α = 0.67 in CHCl3). The enantiomeric excess was determined by HPLC analysis on Daichel Chiralpak IA column (n-hexane/i-
PrOH = 75:25, 1 mL/min), λ = 225 nm, τmajor = 13.22 min, τminor = 22.00 min, ee = 95%.

(656α,6α,12αR)-9-Fluoro-6-phenyl-6α,12α-dihydro-6H,7-H
benzo[4,5]isothiazolo[2,3-α]chromeno[3,2-e]pyridine 14,14-
Dioxide (6d). White solid (29 mg, 70%); 1H NMR (500 MHz,
CDCl3) δ 7.87 (d, J = 7.8 Hz, 1H), 7.69–7.64 (m, 2H), 7.60–
7.57 (m, 1H), 7.39–7.31 (m, 3H), 7.17 (d, J = 7.2 Hz, 2H),
6.91–6.86 (m, 2H), 6.74 (d, J = 8.2 Hz, 1H), 6.00 (s, 1H),
5.73 (d, J = 2.1 Hz, 1H), 3.57 (d, J = 10.0 Hz, 1H), 3.04 (dd,
J = 17.2, 5.8 Hz, 1H), 2.65 (d, J = 17.2 Hz, 1H), 2.53–
2.42 (m, 1H). 13C NMR (125 MHz, CDCl3) δ 158.5, 156.7,
148.1, 141.9, 133.2, 133.4, 130.3, 129.8, 128.6, 128.4,
127.6, 121.4, 121.3, 119.9, 119.9, 118.6, 118.5, 115.1, 115.1,
115.0, 114.8, 104.0, 76.6, 39.6, 37.1, 27.7. ESI-HRMS: [M +
H]+ calcld. For C22H18FNO3S2 m/z: 420.1064; found: 420.1066. (α = 1.92 in CHCl3). The enantiomeric excess was determined by HPLC analysis using a Daichel Chiralpak IA column (n-hexane/i-
PrOH = 75:25, 1 mL/min), λ = 225 nm, τmajor = 11.73 min, τminor = 19.69 min, ee = 94%.

(656α,6α,12αR)-9-Methyl-6-phenyl-6α,12α-dihydro-6H,7-H
benzo[4,5]isothiazolo[2,3-α]chromeno[3,2-e]pyridine 14,14-
Dioxide (6f). White solid (31 mg, 75%); 1H NMR (500 MHz,
CDCl3) δ 7.87 (d, J = 7.8 Hz, 1H), 7.68–7.62 (m, 2H), 7.61–
7.57 (m, 1H), 7.38–7.30 (m, 3H), 7.17 (d, J = 7.0 Hz, 2H),
6.97 (d, J = 8.2 Hz, 1H), 6.88–6.79 (m, 2H), 6.00 (d, J = 2.1
Hz, 1H), 5.73 (d, J = 2.6 Hz, 1H), 3.60 (dd, J = 10.3, 2.4 Hz,
1H), 3.02 (dd, J = 17.0, 5.9 Hz, 1H), 2.62 (dd, J = 17.1, 2.4
Hz, 1H), 2.49–2.41 (m, 1H), 2.27 (s, 3H). 13C NMR (125 MHz,
CDCl3) δ 149.3, 143.1, 132.1, 132.4, 130.9, 130.2, 129.6,
129.0, 128.9, 128.7, 128.6, 128.5, 127.4, 121.3, 118.2, 117.2,
104.2, 76.5, 39.3, 37.5, 27.6, 20.6. ESI-HRMS: [M +
H]+ calcld. For C22H18FNO3S2 m/z: 416.1315; found: 416.1309. (α = −167.7 (c = 1.17 in CHCl3). The enantiomeric excess was determined by HPLC analysis using a Daichel Chiralpak IA column (n-hexane/i-
PrOH = 75:25, 1 mL/min), λ = 210 nm, τmajor = 11.40 min, τminor = 26.86 min, ee = 99%.

(656α,6α,12αR)-6-Phenyl-6α,12α-dihydro-6H,7-H-benzo[4,5]-
isothiazolo[3′,2′:5,6]pyrido[1,2-c][1,2,3]oxathiazine 14,14-
Dioxide (6i). The reaction was conducted following the general procedure; after it was consumed, the intermediate was purified by flash column chromatography and then dissolved in CHCl3 (1.0 mL). BF3·Et2O (3.0 equiv) was added at 0 °C, the reaction mixture was stirred at 25 °C for 1 h, and the product was purified by column chromatography. White solid (25 mg, 60%); 1H NMR (500 MHz, CDCl3) δ 7.60 (d, J = 7.3 Hz,
1H), 7.42–7.29 (m, 4H), 7.26–7.22 (m, 1H), 7.21–7.16 (m, 4H),
7.04 (d, J = 7.5 Hz, 1H), 6.99–6.89 (m, 2H), 6.11 (d, J =
1.9 Hz, 1H), 5.80 (d, J = 2.4 Hz, 1H), 3.33 (dd, J = 11.7, 2.2
Hz, 1H), 3.06 (dd, J = 17.1, 5.8 Hz, 1H), 2.62 (d, J = 17.1
Hz, 1H), 2.49 (dd, J = 11.7, 5.9 Hz, 1H). 13C NMR (125 MHz,
CDCl3) δ 151.6, 148.4, 141.7, 130.5, 129.5, 129.3, 128.9,
128.5, 128.1, 127.5, 126.4, 124.6, 121.9, 119.5, 118.4, 117.4,
109.5, 80.3, 38.5, 36.2, 27.7. ESI-HRMS: [M + H]+
ACS Omega

Article

calcd. For C_{24}H_{20}NO_{4}S·zHCl: 418.1108; found: 418.1111. {[α]_{D}^{20}} = -133.9 (c = 1.08 in CHCl₃). The enantiomeric excess was determined by HPLC analysis using a Daicel Chiralpak IB column (n-hexane/i-PrOH/CH₂Cl₂ = 75:22:3, 1 mL/min), λ = 225 nm, t_{major} = 13.91 min, t_{minor} = 9.34 min, ee = 98%.

2-((2R,3S,4R)-3-(1,1-Dioxido benzo[d]isothiazol-3-yl)-2-phenylchroman-4-yl)-2-phenylacetaldehyde (7a). Pale yellow solid (30 mg, 71%); ¹H NMR (500 MHz, CDCl₃) δ 9.69 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.39 (dd, J = 11.1, 4.1 Hz, 1H), 7.36 (d, J = 7.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.16–7.10 (m, 3H), 7.07–7.02 (m, 3H), 5.15 (d, J = 9.4 Hz, 1H), 4.36–4.24 (m, 1H), 3.88 (dd, J = 10.7, 9.6 Hz, 1H), 3.16 (dd, J = 17.2, 5.7, 1.3 Hz, 1H), 2.72 (dd, J = 17.3, 4.2, 1.9 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 200.9, 176.8, 154.4, 139.1, 137.5, 133.4, 133.3, 130.8, 128.8, 128.4, 126.8, 126.6, 124.0, 122.5, 122.2, 122.0, 117.7, 81.3, 46.6, 45.6, 36.0. ESI-HRMS: [M + H]^+ calc. For C_{24}H_{20}NO_{4}S·zHCl: 418.1108; found: 418.1105. {[α]_{D}^{20}} = +13.7 (c = 1.25 in CHCl₃). The enantiomeric excess was determined by HPLC analysis using a Daicel Chiralpak IB column (n-hexane/i-PrOH/CH₂Cl₂ = 80:17.3, 1 mL/min), λ = 225 nm, t_{major} = 32.39 min, t_{minor} = 13.77 min, ee = 98%.

2-((2R,3S,4R)-3-(1,1-Dioxido benzo[d]isothiazol-3-yl)-2-(naphthalen-2-yl)chroman-4-yl)-2-phenylacetaldehyde (7b). Yellow solid (24 mg, 51%); ¹H NMR (500 MHz, CDCl₃) δ 9.70 (s, 1H), 7.77 (s, 1H), 7.72–7.63 (m, 2H), 7.61–7.58 (m, 2H), 7.53–7.51 (m, 1H), 7.41–7.23 (m, 5H), 7.13 (t, J = 7.3 Hz, 1H), 7.11–7.01 (m, 3H), 5.33 (d, J = 9.4 Hz, 1H), 4.42–4.24 (m, 1H), 3.98 (dd, J = 10.7, 9.6 Hz, 1H), 3.19 (dd, J = 17.2, 5.6, 1.2 Hz, 1H), 2.73 (dd, J = 17.3, 4.1, 1.9 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 200.9, 176.8, 154.4, 138.9, 134.7, 133.2, 133.1, 130.7, 129.3, 128.8, 128.6, 128.4, 128.0, 127.3, 126.8, 126.4, 126.6, 124.3, 122.5, 122.1, 122.0, 117.7, 81.5, 46.4, 45.5, 36.0. ESI-HRMS: [M + H]^+ calc. For C_{24}H_{20}NO_{4}S·zHCl: 468.1264; found: 468.1267. {[α]_{D}^{20}} = -12.9 (c = 0.83 in CHCl₃). The enantiomeric excess was determined by HPLC analysis using a Daicel Chiralpak IB column (n-hexane/i-PrOH/CH₂Cl₂ = 80:17.3, 1 mL/min), λ = 225 nm, t_{major} = 23.12 min, t_{minor} = 12.04 min, ee = 99%.

2-((2R,3S,4R)-3-(1,1-Dioxido benzo[d]isothiazol-3-yl)-6-fluoro-2-phenylchroman-4-yl)-2-phenylacetaldehyde (7c). Pale yellow solid (33 mg, 75%); ¹H NMR (500 MHz, CDCl₃) δ 9.68 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.3 Hz, 2H), 7.17–7.07 (m, 3H), 7.04 (t, J = 7.4 Hz, 1H), 7.01–6.98 (m, 2H), 6.94 (td, J = 8.3, 2.6 Hz, 1H), 5.10 (d, J = 9.4 Hz, 1H), 4.28–4.19 (m, 1H), 3.90 (dd, J = 10.6, 9.6 Hz, 1H), 3.14 (dd, J = 17.7, 5.6, 1.0 Hz, 1H), 2.73 (dd, J = 17.8, 4.1, 1.4 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 200.3, 176.6, 158.6, 156.7, 150.5, 139.1, 137.3, 133.5, 133.3, 130.7, 128.9, 126.8, 126.4, 122.0, 118.9, 118.8, 115.4, 115.2, 113.0, 112.8, 81.5, 46.2, 45.5, 36.0. ESI-HRMS: [M + H]^+ calc. For C_{25}H_{22}NO_{3}S·zHCl: 436.1013; found: 436.1009. {[α]_{D}^{20}} = +48.1 (c = 1.17 in CHCl₃). The enantiomeric excess was determined by HPLC analysis using a Daicel Chiralpak IB column (n-hexane/i-PrOH/CH₂Cl₂ = 80:17.3, 1 mL/min), λ = 225 nm, t_{major} = 16.32 min, t_{minor} = 12.03 min, ee = 99%.

2-((2R,3S,4R)-2-(2-Dioxido-1H-benzo[b]isothiazol-3-yl)-2-phenylchroman-4-yl)-2-phenylacetaldehyde (7d). Yellow solid (36 mg, 84%); ¹H NMR (500 MHz, CDCl₃) δ 9.70 (s, 1H), 7.54–7.49 (m, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 7.4 Hz, 2H), 7.30 (d, J = 7.9 Hz, 1H), 7.23 (t, J = 7.7 Hz, 1H), 7.17–7.10 (m, 3H), 7.10–7.00 (m, 4H), 5.10 (d, J = 9.2 Hz, 1H), 4.29–4.21 (m, 1H), 4.14–4.05 (m, 1H), 3.20 (dd, J = 9.2, 5.7 Hz, 1H).
The reaction was extracted with water and ethyl acetate three times.

The enantiomeric excess was determined by HPLC analysis using a Daicel Chiralpak IB column (n-hexane/i-PrOH/CH2Cl2 = 80:17:3, 1 mL/min), λ = 260 nm, t_major = 11.05 min, t_minor = 8.49 min, ee = 97%.

Synthesis of Compound 10. (E)-4-((2R,3S,4R)-3-(1,1-Dioxido-benzo[d]isothiazol-3-yl)-2-phenylchroman-4-yl)-1-phenylbut-2-en-1-one (9). The reaction was conducted with 2a (0.50 mmol, 1.0 equiv) and 3a (32 mg, 0.11 mmol) in CHCl3 (3.0 mL) at 25 °C, and then 1a (0.60 mmol, 1.2 equiv) was added. After the reaction was completed, Ph3P=CHCOPh was added. After the reaction was completed, Ph3P=CHCOPh was added. The product was purified by column chromatography on silica gel to provide product 9 as a yellow solid (175 mg, 67%). 1H NMR (500 MHz, CDCl3) δ 7.70 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.3 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.45–7.41 (m, 2H), 7.36–7.32 (m, 4H), 7.28–7.23 (m, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.11–7.07 (m, 3H), 7.05 (d, J = 8.1 Hz, 1H), 6.99 (s, J = 7.4 Hz, 1H), 6.93 (s, J = 7.7 Hz, 1H), 6.83 (dd, J = 15.1, 8.7, 6.3 Hz, 1H), 6.59 (d, J = 15.3 Hz, 1H), 5.16 (s, J = 9.4 Hz, 1H), 4.28–4.20 (m, 1H). 13C NMR (125 MHz, CDCl3) δ 189.1, 176.6, 154.7, 143.9, 139.1, 137.5, 130.7, 130.3, 128.9, 128.7, 128.5, 128.4, 128.3, 127.1, 126.3, 127.2, 122.2, 122.0, 117.8, 81.0, 46.6, 39.2, 35.2.

**REFERENCES**

(1) For books, see: (a) Zanardi, F.; Rassu, G.; Battistini, L.; Curti, C.; Sartori, A.; Casiraghi, G.; Attanasi, A. Targets in Heterocyclic Chemistry—Chemistry and Properties; Orazio, A. A.; Spinelli, D., Eds.; Societá Chimica Italiana: Rome, Italy, 2012; Vol. 16. (b) Johnson, C. D.; Balasubramanian, M.; Keay, J. G.; Hepworth, J. D.; Green, G. R. Comprehensive Heterocyclic Chemistry II, 2nd ed.; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, pp 1–500. (c) Alvarez-Builla, J. Modern Heterocyclic Chemistry; Vaquero, J. J.; Barluenga, J., Eds.; Wiley-VCH: Weinheim, Germany, 2011; pp 1–9. (d) Heterocyclic Chemistry in Drug Discovery; Li, J.-J., Ed.; Wiley: Hoboken, NJ, 2013; pp 1–16. (e) Kiu, P.; Ylil-Kauhaluoma, J. Heterocycles in Natural Product Synthesis; Majumdar, K. C.; Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2011; pp 267–297. (f) Heterocyclic Chemistry, 4th ed.; Joule, J. A.; Mills, K., Eds.; John Wiley & Sons, 2013; pp 629–664.

(2) For selected reviews, see: (a) Zhou, J. Recent advances in multicomponent catalytic asymmetric tandem reactions. Chem. - Asian J. 2010, 5, 422–434. (b) Grondal, C.; Jeanty, M.; Enders, D. Organocatalytic cascade reactions as a new tool in total synthesis. Nat. Chem. 2010, 2, 167–178. (c) Albrecht, L.; Jiang, H.; Jørgensen, K. A. Simple recipe for sophisticated cocktails: organocatalytic one-pot reactions—concept, nomenclature, and future perspectives. Angew. Chem., Int. Ed. 2011, 50, 8492–8509. (d) Pellissier, J. Recent developments in asymmetric organocatalytic domino reactions. Adv. Synth. Catal. 2012, 354, 237–294. (e) Volla, C. M. R.; Atodiresei, L.; Rueping, M. Catalytic C–C bond-forming multicomponent cascade or domino reactions: pushing the boundaries of complexity in asymmetric organocatalysis. Chem. Rev. 2014, 114, 2390–2431. (f) Wang, Y.; Lu, H.; Xu, P.-F. Asymmetric catalytic cascade reactions for constructing diverse scaffolds and complex molecules. Acc. Chem. Res. 2015, 48, 1832–1844.
(3) For reviews, see: (a) Boger, D. L. Diels-Alder reactions of azadienes. *Tetrahedron* 1983, 39, 2869–2939. (b) Boger, D. L. Diels-Alder reactions of heterocyclic azadienes. *Scope and applications. Chem. Rev. 1986, 86, 781–793. (c) Behforouz, M.; Ahmadian, M. Diels-Alder reactions of 1-azadienes. *Tetrahedron* 2000, 56, 5259–5288. (d) Groennadal, B.; Ruijter, E.; Orru, R. V. A. 1-Azadienes in cyclodaddition and multicomponent reactions towards N-heterocycles. *Chem. Commun. 2008, 5474–5489. (e) Shimizu, M.; Hachiya, I.; Mizota, I. Conjugated imines and iminium salts as versatile acceptors of nucleophiles. *Chem. Commun. 2009, 874–889. (f) Monhal, J.-C.; Masschelein, K. G. R.; Stevens, C. V. Electron-deficient 1- and 2-azabuta-l,3-dienes: a comprehensive survey of their synthesis and reactivity. *Chem. Soc. Rev. 2011, 40, 4708–4739.* (g) Jiang, X.; Wang, R. Recent developments in catalytic asymmetric inverse-electron-demand Diels–Alder reaction. *Chem. Rev. 2013, 113, 5515–5546.

(4) For stereoselective azadiene–Diels-Alder reactions of electron-deficient 1-azadienes, see: (a) Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. Diastereo- and enantioselective cascade process. Enantio- and diastereoselective synthesis of tetrahydrofuro-2,3-b]uran-2(3H)-one derivatives and related oxygen heterocycles via an asymmetric organocatalytic cascade process. *Org. Chem. Front. 2017, 4, 2358–2363.* (b) Wu, X.-N.; You, Z.-H.; Liu, Y.-K. Different hybridized oxygen atoms controlled chemoselective formation of oxocarbonium ions: synthesis of chiral heterocyclic compounds. *Org. Biomol. Chem. 2018, 16, 6507–6520.* (7) (a) Breschi, M. C.; Calderone, V.; Martelli, A.; Minutolo, F.; Rapposelli, S.; Testai, L.; Tonelli, F.; Balsamo, A. New benzyropnyl-based openers of the mitochondrial ATP-sensitive potassium channel with potent anti-ischemic properties. *J. Med. Chem. 2006, 49, 7600–7602. (b) Khellili, S.; Florence, X.; Bouhadja, M.; Abdelaziz, S.; Mechouch, N.; Mohamed, Y.; de Tullio, P.; Lebrun, P.; Pirrotte, B. Synthesis and activity on rat aorta rings and rat pancreatic β-cells of ring-opened analogues of benzyropnyl-type potassium channel activators. *Bioorg. Med. Chem. 2008, 16, 6124–6130.* (c) Cui, A.; Bianucci, A. M.; Calderone, V.; Testai, L.; Digiacomo, M.; Rapposelli, S.; Balsamo, A. Predictive models, based on classification algorithms, for compounds potentially active as mitochondrial ATP-sensitive potassium channel openers. *Bioorg. Med. Chem. 2009, 17, 5565–5571.* (8) (a) Sun, X.-L.; Chen, Y.-H.; Zhu, D.-Y.; Zhang, Y.; Liu, Y.-K. Substrate-controlled, one-pot synthesis: access to chiral chramon-2-one and polycyclic derivatives. *Org. Lett. 2016, 18, 864–867. (b) Chen, Y.-H.; Sun, X.-L.; Guan, H.-S.; Liu, Y.-K. Diversity-oriented one-pot synthesis to construct functionalized chramon-2-one derivatives and other heterocyclic compounds. *J. Org. Chem. 2017, 82, 4774–4783.* (9) (a) Zu, L.; Zhang, S.; Xie, H.; Wang, W. Catalytic asymmetric oxa-Michael–Michael cascade for facile construction of chiral chramons via an aminal intermediate. *Org. Lett. 2009, 11, 1627–1630. (b) Ramachary, D. B.; Shiva Prasad, M.; Vijaya Laxmi, M.; Madhavarachy, R. Asymmetric synthesis of drug-like spiro[chroman-3,3′-indolin]-2′-ones through aminal-catalysis. *Org. Biomol. Chem. 2014, 12, 574–580.* (10) (a) You, Z.-H.; Chen, Y.-H.; Liu, Y.-K. From racemic precursors to fully stereocontrolled products: one-pot synthesis of chiral α-amino lactones and lactams. *Org. Biomol. Chem. 2016, 14, 6316–6327. (b) Li, Z.-L.; Liu, C.; Tan, R.; Tong, Z.-P.; Liu, Y.-K. Organocatalytic asymmetric [2 + 2 + 2] annulation to construct six-membered spirocyclic oxindoles with six continuous stereogenic centers. *Catalysts 2016, 6, 65–78.* (c) Cai, P.-W.; You, Z.-H.; Xie, L.-H.; Tan, R.; Tong, Z.-P.; Liu, Y.-K. The attractive application of lactic chemistry: from racemic lactol to natural product skeleton. *Synthesis 2016, 48, 2581–2594.* (d) Liu, C.; Liu, Y.-K. Asymmetric organocatalytic one-pot, two-step sequential process to synthesize chiral acetal-containing polycyclic derivatives from cyclic hemiacetals and enones. *J. Org. Chem. 2017, 82, 10450–10460.* (e) You, Z.-H.; Chen, Y.-H.; Wu, X.-N.; Liu, Y.-K. Lactols in asymmetric sequencial organo- and Gold-Catalysis: synthesis of densely functionalized epimeric bicyclic O,C-acetals. *Adv. Synth. Catal. 2017, 359, 4260–4266.* (f) Qiao, L.; Duan, Z.-W.; Wu, X.-N.; Li, D.-H.; Gu, Q.-Q.; Liu, Y.-K. Organocatalytic diversity-oriented asymmetric synthesis of structurally and stereochemically complex heterocycles. *Org. Lett. 2018, 20, 1630–1633.* (g) Pei, J.-P.; Chen, Y.-H.; Liu, Y.-K. Asymmetric organocatalytic sequential reaction of structurally complex cyclic hemiacetals and functionalized nitro-olefins to synthesize diverse heterocycles. *Org. Lett. 2018, 20, 3609–3612.* (11) (a) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. Metal-free, organocatalytic asymmetric transfer hydrogenation of α,β-unsaturated aldehydes. *Angew. Chem., Int. Ed. 2005, 44, 108–110.* (b) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. A metal-free transfer hydrogenation: organocatalytic conjugate reduction of α,β-unsaturated aldehydes. *Angew. Chem., Int. Ed. 2004, 43, 6660–6662.* (c) Ouellet, S. G.; Tuttle, J. B.; Macmillan, D. W. C. Enantioselective organocatalytic hydride reduction. *J. Am. Chem. Soc. 2005, 127, 32–33.* (d) Mayer, S.; List, B. Asymmetric counteranion-directed catalysis. *Angew. Chem., Int. Ed. 2006, 45, 4193–4195.* (e) Tuttle, J. B.; Ouellet, S. G.; Macmillan, D. W. C. Organocatalytic transfer hydrogenation of cyclic enones. *J. Am. Chem. Soc. 2006, 128, 12620–12621.* (f) Macmillan, N. J. A.; List, B. Highly enantioselective transfer hydrogenation of α,β-unsaturated ketones. *J. Am. Chem. Soc. 2006, 128, 13368–13369.* (12) For selected reviews, see: (a) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. Enantioselective organocatalytic transfer hydrogenation reactions using Hantzsch esters. *Acc. Chem. Res.*
Advances in catalytic metal-free reductions: from bio-inspired concepts to applications in the organocatalytic synthesis of pharmaceuticals and natural products. *Green Chem.* 2011, 13, 1084–1105. (c) de Vries, J. G.; Mršić, N. Organocatalytic asymmetric transfer hydrogenation of imines. *Catal. Sci. Technol.* 2011, 1, 727–735. (d) Shi, F.; Gong, L.-Z. Relay catalysis enables hydrogen gas to participate in asymmetric organocatalytic hydrogenation. *Angew. Chem., Int. Ed.* 2012, 51, 11423–11425. (e) Zheng, C.; You, S.-L. Transfer hydrogenation with Hantzsch esters and related organic hydride donors. *Chem. Soc. Rev.* 2012, 41, 2498–2518. (f) McSkimming, A.; Colbran, S. B. The coordination chemistry of organo-hydride donors: new prospects for efficient multi-electron reduction. *Chem. Soc. Rev.* 2013, 42, 5439–5488. (g) Pinaki, B. S.; Zhihua, S. Axially chiral Brønsted acid catalyzed transformations of electrophilic imines. *Curr. Org. Chem.* 2014, 18, 127–150. (h) Foubelo, F.; Yus, M. Catalytic asymmetric transfer hydrogenation of imines: recent advances. *Chem. Rev.* 2015, 15, 907–924. (i) Phillips, A. M. F.; Pombeiro, A. J. L. Recent advances in organocatalytic enantioselective transfer hydrogenation. *Org. Biomol. Chem.* 2017, 15, 2307–2340.