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Merging Chiral Brønsted Acid/Base Catalysis: An Enantioselective [4 + 2] Cycloaddition of *o*-Hydroxystyrenes with Azlactones

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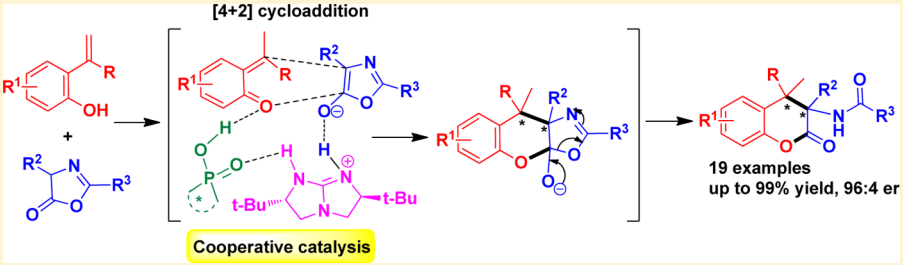
Supporting Information

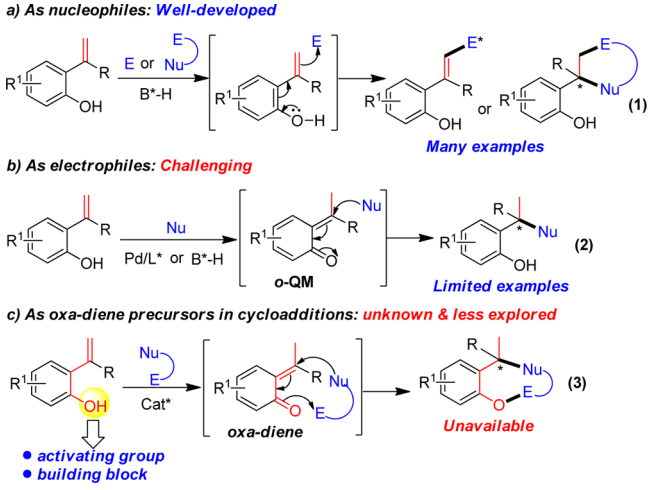


ABSTRACT: An enantioselective [4 + 2] cycloaddition of *o*-hydroxylstyrenes with azlactones has been established by merging chiral Brønsted acid (chiral phosphoric acid) and base (chiral guanidine) catalysis, which constructed a biologically important dihydrocoumarin scaffold in an efficient and enantioselective style (up to 99% yield, 96:4 er). This approach has not only realized the successful application of *o*-hydroxylstyrenes as oxa-diene precursors in catalytic asymmetric cycloadditions but also established a new cooperative catalytic system of chiral phosphoric acid and chiral guanidine.

INTRODUCTION

In recent years, *o*-hydroxylstyrenes have exhibited their great potential as a type of versatile reactant in asymmetric catalysis and synthesis (Scheme 1).[1−4] In these transformations, the *o*-hydroxyl group serves as an activating group, which played a crucial role in both the reactivity and the enantioselectivity by its interaction with chiral catalysts. In most cases, *o*-hydroxylstyrenes are activated by chiral Brønsted acid (B*−H) to act as nucleophiles, thus performing vinylogous nucleophilic reactions with various electrophiles (E) to give substitution or cycloaddition products in an enantioselective fashion (eq 1).[1] However, in contrast to these well-developed transformations that utilized *o*-hydroxylstyrenes as nucleophiles, the catalytic asymmetric reactions employing this class of substrates as electrophiles are still under-developed and rather challenging (eq 2).[3,4] In this research field, Sigman and co-workers pioneered the application of *o*-hydroxylstyrenes in asymmetric catalysis by converting them into *o*-quinone methide (*o*-QM) intermediates in the presence of Pd/chiral ligands, which could be attacked by a variety of nucleophiles to afford enantioenriched products.[3] Very recently, Sun et al. discovered that the *o*-QM intermediates could also be generated from *o*-hydroxylstyrenes under the catalysis of B*−H, which were readily attacked by nucleophilic Hantzsch esters or indoles in an enantioselective way.[4a] Although these elegant works have realized the conversion of *o*-hydroxylstyrenes into *o*-QMs, which should be promising oxa-dienes for catalytic enantioselective cycloadditions,[5] the use of o-hydroxylstyrenes as oxa-diene precursors in catalytic asymmetric cycloadditions still remains unknown and less explored (eq 3). Nevertheless, this class of transformations is highly valuable because the hydroxyl group in *o*-hydroxylstyrenes will not only act as an activating group but also serve as a building block. More importantly, it will also explore a new direction for *o*-hydroxylstyrene-involved enantioselective reactions and provide

Scheme 1. Profile of *o*-Hydroxylstyrene-Involved Catalytic Enantioselective reactions



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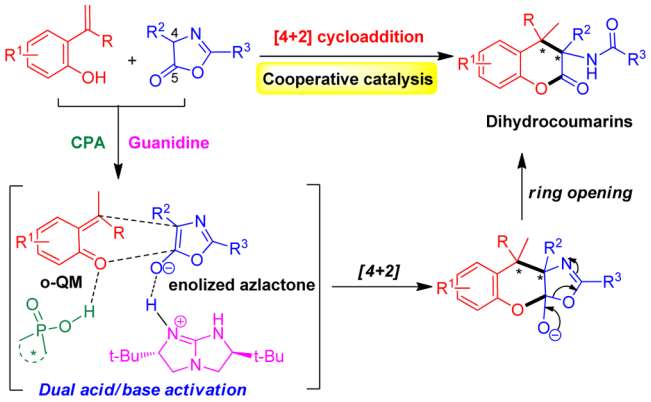
an efficient strategy for constructing oxygenous cyclic frameworks with optical purity.

To realize the application of *o*-hydroxylstyrenes as oxa-diene precursors in catalytic asymmetric cycloadditions, a specific synthetic design is highly desired, which requires the selection of a suitable reaction partner possessing both the nucleophilic and the electrophilic sites in the structure of one molecule. In this context, azlactones arouse our great interests because this substrate class has the nucleophilic and electrophilic sites at C4 and C5-positions,[6] respectively, which can principally perform an enantioselective cycloaddition reaction with oxa-dienes generated from *o*-hydroxylstyrenes in the presence of chiral catalysts. Among different chiral catalysts, chiral phosphoric acid[7] (CPA) belongs to a significant class of chiral Brønsted acid, which can promote the transformation of *o*-hydroxylstyrenes into *o*-QMs.[4] On the other hand, chiral guanidines,[8−10] as a typical type of chiral Brønsted bases, are able to facilitate the formation of enolized azlactones.[6] So, we envision whether we can combine the catalysis of CPA and chiral guanidine in a synergistic way, thus simultaneously activating the two substrates of *o*-hydroxylstyrene and azlactone to undergo an enantioselective [4 + 2] cycloaddition and a subsequent ring opening, which will finally construct a biologically important dihydrocoumarin scaffold[11] in an enantioenriched fashion (Scheme 2). Although the combined catalysis of CPA with

Scheme 2. Design of the [4 + 2] Cycloadditions



other catalysts is flourishing in recent years and has proven to be a robust method to achieve enantioselective transformations that can hardly be paralleled by monocatalyst system,[7,12] the cooperative catalysis of CPA as a Brønsted acid with chiral guanidine as a Brønsted base has not been explored yet, mainly because there exist great challenges in this combination. The first one is to realize the compatibility of the two catalysts, which possess the opposite acidic/basic property. The second one is to make the two chiral catalysts generate a matched interaction in stereoselective control. So, it is highly desirable, but rather challenging, to establish a synergistic catalyst system of CPA and chiral guanidine.

Considering these challenges and based on our previous works on asymmetric organocatalysis,[13] we tried this designed [4 + 2] cycloaddition and successfully accomplished this task. Herein, we report the catalytic enantioselective cycloaddition of *o*-hydroxylstyrenes with azlactones, which has not only realized the successful application of *o*-hydroxylstyrenes as oxa-diene precursors in catalytic asymmetric cycloadditions but also established a new cooperative catalytic system of CPA and chiral guanidine. By using this unprecedented strategy, biologically important dihydrocoumarin scaffold has been constructed in an efficient and enantioselective style (up to 99% yield, 96:4 er).

RESULTS AND DISCUSSION

Initially, the reaction of *o*-hydroxylstyrene **1a** with azlactone **2a** was employed to certify our hypothesis in the presence of BINOL-derived CPA **4a** as a monocatalyst at 80 °C, which smoothly afforded the designed [4 + 2] cycloaddition product **3aa** in a good yield but without chiral induction (Table 1, entry 1). The subsequent screening of this type of CPA, **4a**−**4f** (entries 1−6), revealed that catalyst **4e** with a bulky 9-anthracenyl group at the 3,3′-position of the BINOL backbone was the best one to deliver the highest enantioselectivity among them (entry 5 vs entries 1−4 and 6), but the enantioselectivity was still very low in this monocatalytic system. Then, we added chiral guanidine **6** as a cocatalyst to the reaction system that we designed, which indeed greatly improved the enantioselectivity to a much higher level of 85:15 er (entry 8 vs 7). This result implied that the two catalysts with the opposite acidic/basic property could be compatible and the binary catalytic system had a synergistic effect on controlling the enantioselectivity. To check whether the absolute configuration of the two catalysts match with each other or not, *ent*-**4e** was utilized to combine with guanidine **6**, which showed inferior catalytic activity to the combination of **4e** with **6** (entry 9 vs 8). This outcome indicated that the matched interaction between the two chiral catalysts played an important role in efficiently catalyzing the reaction. Besides, we also tried using a variety of chiral thiourea or squaramide-based tertiary amines **7** and **8** (see Supporting Information for details) as bifunctional Brønsted bases to combine with CPA **4e** or *ent*-**4e**. Nevertheless, none of these combinations exhibited higher capability than the combination of **4e** with **6** in terms of the enantioselective control (entry 10 vs 8), which demonstrated the superiority of the combined catalytic system of CPA **4e** with chiral guanidine **6**. In order to further enhance the enantioselectivity, we changed the backbone of CPA **4e** from BINOL to structurally more rigid SPINOL with the same stereo-orientation (entry 11). In the presence of this SPINOL-derived CPA **5**, subsequent condition optimizations, such as screening solvents, additives, temperatures, reagents ratios, and catalyst loading were carried out (entries 12−14; see the Supporting Information for details). Finally, the optimal reaction condition was found out, which generated the desired product **3aa** in a high yield of 84% and the best enantioselectivity of 93:7 er (entry 13).

After establishing the optimal reaction conditions, we performed the investigation on the substrate scope of *o*-hydroxylstyrenes **1**. As shown in Table 2, this strategy of cooperative catalysis was applicable to a series of *o*-hydroxylstyrenes **1** bearing electronically different R groups on the phenyl ring, which competently acted as oxa-diene precursors in the designed [4 + 2] cycloadditions and offered the dihydrocoumarin products **3** in good yields and moderate to good enantioselectivities. Generally, the electronic nature of the substituents had no obvious effect on the enantioselectivity, because there was no remarkable difference among *o*-hydroxylstyrenes **1** bearing either electron-withdrawing groups (**3ba**−**3da**) or electron-donating ones (**3ea**−**3ga**) with regard to the enantioselectivity. Besides, the position of the substituents also seemed to have no influence on the enantioselectivity, but it affected the yield to some extent (**3ba** vs **3ha**). Notably, the alkyl R^1 group could be elongated

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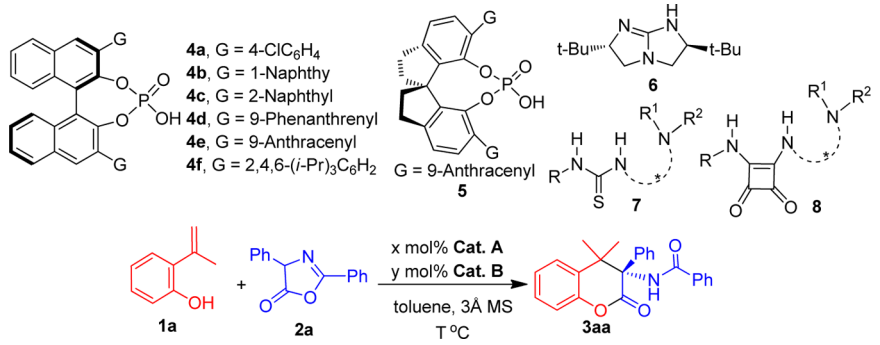
Table 1. Optimization of the Conditions[a]



entry	cat. A (x, mol %)	cat. B (y, mol %)	T (°C)	yield (%)[b]	er (%)[c]
1	**4a** (10)	–	80	73	50:50
2	**4b** (10)	–	80	63	52:48
3	**4c** (10)	–	80	42	52:48
4	**4d** (10)	–	80	99	56:44
5	**4e** (10)	–	80	99	65:35
6	**4f** (10)	–	80	78	53:47
7	**4e** (20)	–	40	99	77:23
8	**4e** (20)	**6** (10)	40	70	85:15
9	*ent*-**4e** (20)	**6** (10)	40	54	17:83
10	**4e** (20) or *ent*-**4e** (20)	**7** or **8** (10)	40	18–99	59:41–84:16
11	**5** (20)	**6** (10)	40	70	87:13
12[d]	**5** (20)	**6** (10)	40	99	88:12
13[d]	**5** (20)	**6** (10)	30	84	93:7
14[d]	**5** (10)	**6** (5)	30	78	91:9

[a]Unless indicated otherwise, the reaction was carried out in 0.05 mmol scale in toluene (1 mL) with 3 Å molecular sieves (MS) (50 mg) at T (°C) for 16 h, and the mole ratio of **1a**:**2a** was 1.5:1. [b]Isolated yield. [c]The ee value was determined by HPLC. [d]Anhydrous $MgSO_4$ (50 mg) was used as additive instead of 3 Å MS.

from a methyl group to an ethyl group, which produced the corresponding [4 + 2] cycloaddition products **3ia** and **3ja** in excellent diastereoselectivities and acceptable enantioselectivities, albeit with moderate yields. However, when we increased the size of the R^1 group or reduced it to the smallest hydrogen atom, no desired [4 + 2] cycloaddition products **3ka** and **3la** were detected. We have made great efforts to perform such reactions by elevating the reaction temperature or elongating the reaction time, but only some unidentified byproducts were observed, which were deduced to be decomposed from azlactones.

Then, the substrate scope with respect to azlactones **2** was further explored. As illustrated in Table 3, this protocol was amenable to a wide range of azlactones **2** with various aromatic R/R^1 substituents, delivering chiral dihydrocoumarin derivatives **3** in generally high yields and good enantioselectivities. The aromatic R group could be altered from an electronically neutral phenyl group (**3aa**) to electronically poor ones (**3ab**–**3ac**), although the enantioselectivity was slightly decreased. As to an aromatic R^1 group, it seemed that the electronically rich ones (**3ad**–**3ag**) were superior to their electronically poor counterparts (**3ah**–**3ai**) with regard to the enantioselective control. Moreover, in some cases, the position of the substituents also exerted an obvious effect on the enantioselectivity (**3ah** vs **3ai**). We also tried to employ aliphatic R/R^1 groups as substituents of azlactones, but these substrates failed to afford the corresponding [4 + 2] cycloaddition products **3aj**–**3al**. Although aliphatic R/R^1 groups could not serve as suitable substituents, the variation of different aromatic R/R^1 groups could still provide the dihydrocoumarin products **3** with structural diversity.

The absolute configuration of product **3aa** (99:1 er after recrystallization) was unambiguously determined to be *S* by single crystal X-ray diffraction analysis (in Scheme 3).[14] The absolute configuration of other products **3** were assigned by analogy. Besides, the relative configuration of product **3ja** was identified by NOE (see Supporting Information for details).

In order to gain some insights into the cooperative catalytic mode of CPA **5** and chiral guanidine **6**, we carried out some control experiments (Table 4). First, the model reaction was performed in the presence of monocatalyst **5** or **6** under the optimal reaction conditions, which just gave the desired products **3aa** in low yields and moderate enantioselectivities (entries 2 and 3). These results indicated that the monocatalytic system was much inferior to the combined catalytic system of CPA **5** and chiral guanidine **6** (entries 2 and 3 vs entry 1). Second, CPA **5** was combined with achiral guanidine **9** to catalyze the reaction (entry 4). Although this combination could also catalyze the formation of product **3aa**, the enantioselectivity was decreased to some extent in comparison with the monocatalytic system of CPA **5** (entry 4 vs 2). Furthermore, chiral guanidine **6** was also integrated with achiral Brønsted acid **10**, which catalyzed the reaction in an efficient way but with no chiral induction (entry 5). These phenomena implied that the chirality of both CPA **5** and chiral guanidine **6** played a crucial role in attaining a high enantioselectivity, and the two chiral catalysts generated a synergistic and matched interaction in controlling the enantioselectivity.

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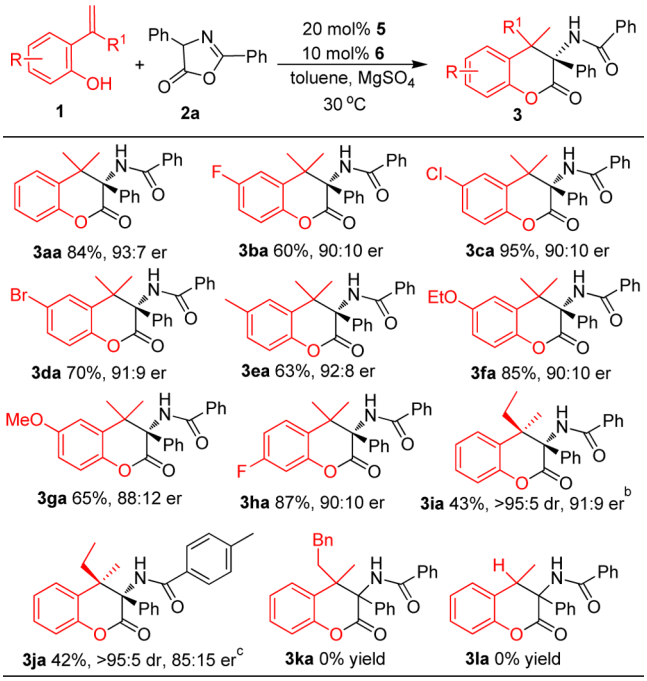
Table 2. Substrate Scope of *o*-Hydroxylstyrenes 1[a]

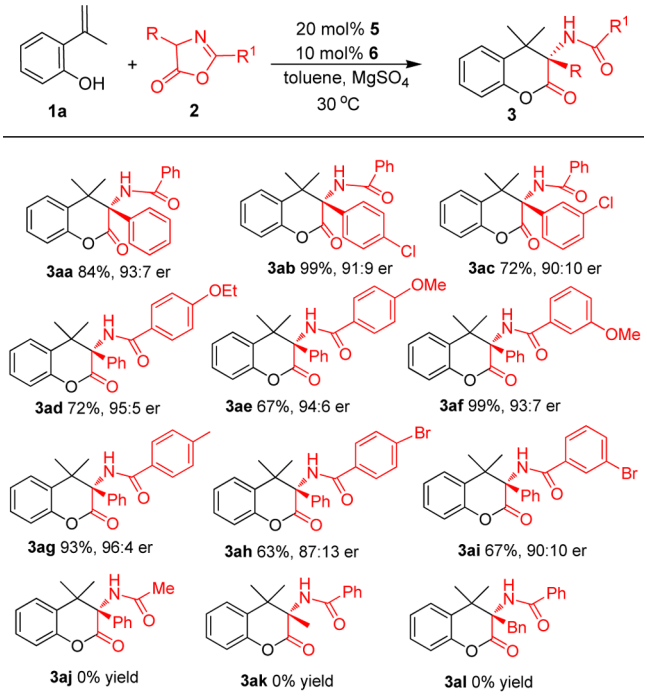


[a]Unless otherwise indicated, the reaction was carried out at 0.05 mmol scale catalyzed by 20 mol % **5** and 10 mol % **6** in toluene (1 mL) with $MgSO_4$ (50 mg) at 30 °C for 16 h, and the mole ratio of **1**:**2a** was 1.5:1. The yields refer to isolated yields, and the er value was determined by HPLC. [b]Performed at 50 °C for 48 h, and the dr value was determined by ^{1}H NMR. [c]Performed at 50 °C for 72 h, and the dr value was determined by ^{1}H NMR.

Moreover, for the aim to investigate the interaction between CPA and chiral guanidine, we premixed the two catalysts (the mole ratio of CPA **5** to guanidine **6** is 2:1 or 1:1) under the standard reaction conditions. In principle, the formation of a salt is anticipated, due to the large pK_a difference between the two catalysts. However, no obvious salts were observed by TLC monitoring of the combined catalyst system. Then, the mixture of the catalysts was further subjected to ^{1}H NMR analysis, which revealed that the chemical shifts of some peaks in the combined catalysts were different from those of the the single catalysts (see Supporting Information for details). Besides, the ^{1}H NMR spectra of the mixed catalysts either with 2:1 or 1:1 mol ratio were nearly the same, which suggested that the active catalyst state under these conditions is similar. So, we deduced that if no salts were formed, there might be a hydrogen bond generated between the two catalysts, because the chemical shifts of some peaks in the ^{1}H NMR spectrum of the combined catalysts were different from that of the individual catalysts.

On the basis of the above control experiments and investigation on the premixed catalysts, we suggested a possible activation mode of the combined catalysts to the substrates. As exemplified by the formation of **3aa** in Scheme 3, chiral spiro-phosphoric acid **5** and chiral guanidine **6** simultaneously activated the oxa-diene intermediate generated in situ from *o*-hydroxylstyrene and enolized azlactone via a hydrogen-bonding interaction. The two catalysts respectively played their important role in activating both of the two intermediates. Besides, a hydrogen bond was formed between the phosphoryl oxygen of CPA **5** and the N–H group of chiral guanidine **6**. This hydrogen bond might contribute greatly to the observed

Table 3. Substrate Scope of Azlactones 2[a]



[a]Unless otherwise indicated, the reaction was carried out at 0.05 mmol scale catalyzed by 20 mol % **5** and 10 mol % **6** in toluene (1 mL) with $MgSO_4$ (50 mg) at 30 °C for 16 h, and the mole ratio of **1a**:**2** was 1.5:1. The yields refer to isolated yields, and the er value was determined by HPLC.

Scheme 3. Suggested Activation Mode and Transition State

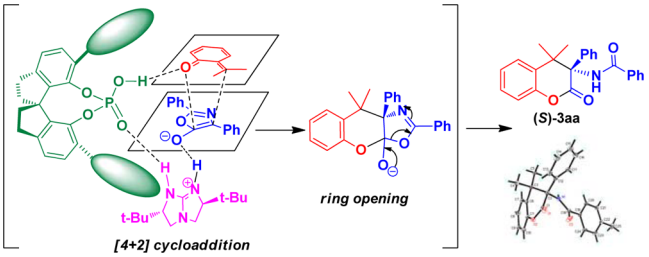
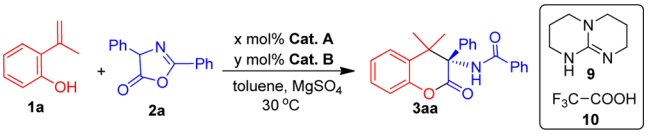


Table 4. Control Experiments[a]



entry	cat. A (*x*, mol %)	cat. B (*y*, mol %)	yield (%)	er (%)
1	**5** (20)	**6** (10)	84	93:7
2	**5** (20)	–	54	77:23
3	–	**6** (10)	45	77:23
4	**5** (20)	**9** (10)	60	70:30
5	**10** (20)	**6** (10)	99	50:50

[a]Unless otherwise indicated, the reaction was carried out at the 0.05 mmol scale in toluene (1 mL) with $MgSO_4$ (50 mg) at 30 °C for 16 h, and the mole ratio of **1a**:**2a** was 1.5:1. The yields refer to isolated yields, and the er value was determined by HPLC.

synergistic and matched interaction between them in controlling the enantioselectivity. Due to the chiral environ-

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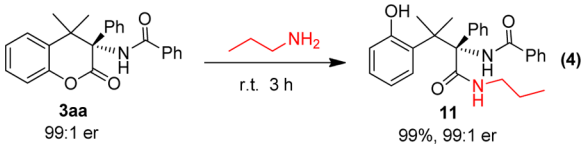
ment created by the two catalysts and their matched orientation, an enantioselective concerted [4 + 2] cycloaddition[6b,e] and a subsequent ring opening took place, which resulted in the experimentally observed product (*S*)-**3aa**.

Finally, due to the biological importance of dipeptides,[15] a preliminary derivation of compound **3aa** was performed by its aminolysis with propylamine, which efficiently generated chiral dipeptide mimetic compound **11** in a quantitative yield of 99% and a retained enantioselectivity of 99:1 er (eq 4).



3aa
99:1 er

11
99%, 99:1 er

(4)

CONCLUSIONS

In summary, we have established an enantioselective [4 + 2] cycloaddition of *o*-hydroxylstyrenes with azlactones by merging chiral Brønsted acid and base catalysis, which led to the construction of the biologically important dihydrocoumarin scaffold in an efficient and enantioselective style (up to 99% yield, 96:4 er). This approach has not only realized the successful application of *o*-hydroxylstyrenes as oxa-diene precursors in catalytic asymmetric cycloadditions but also established a new cooperative catalytic system of chiral phosphoric acid and chiral guanidine. More importantly, the application of *o*-hydroxylstyrenes as oxa-diene precursors in cycloadditions will not only explore a new direction for *o*-hydroxylstyrene-involved enantioselective reactions but also provide an efficient strategy for constructing oxygenous cyclic frameworks with optical purity. Besides, the synergistic interaction of chiral phosphoric acid and chiral guanidine has offered a unique catalytic system to asymmetric cooperative catalysis, which will find more applications in achieving unusual enantioselective transformations.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively. The solvents used for NMR spectroscopy were $CDCl_3$ and DMSO-d_6, using tetramethylsilane as the internal reference. HRMS (ESI) was determined by a HRMS/MS instrument. Enantiomeric ratios (er) were determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral column used for the determination of enantiomeric excesses by chiral HPLC was Chiralpak IA and IC columns. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line, at the temperatures indicated. The X-ray source used for the single crystal X-ray diffraction analysis of compound **3aa** was Cu Kα (λ = 1.541 78), and the thermal ellipsoid was drawn at the 30% probability level. Analytical grade solvents for the column chromatography and commercially available reagents were used as received. All starting materials commercially available were used directly. Substrates **1** and **2** were synthesized according to the literature method.[1c,6a] The purity of the products was examined by NMR and HPLC spectra.

Typical Procedure for the Synthesis of Products 3. To the mixture of azlactone **2** (0.05 mmol), chiral phosphoric acid **5** (0.01 mmol), chiral guanidine **6** (0.005 mmol), and magnesium sulfate (50 mg) was added a solution of *o*-hydroxylstyrene **1** (0.075 mmol) in toluene (1 mL). After being stirred at 30 °C for 16 h, the reaction mixture was directly purified by flash chromatography to afford pure products **3**.

(S)-N-(4,4-Dimethyl-2-oxo-3-phenylchroman-3-yl)benzamide ***(3aa)***. Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 16 h; yield 84% (15.6 mg); white solid; mp 216−218 °C; $[\alpha]_D^{20}$ = −20 (*c* 0.3, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (d, *J* = 7.2 Hz, 2H), 7.53−7.48 (m, 1H), 7.48−7.44 (m, 1H), 7.44−7.35 (m, 4H), 7.32−7.26 (m, 2H), 7.26−7.21 (m, 3H), 7.12 (s, 1H), 6.96 (dd, *J* = 8.0, 1.5 Hz, 1H), 1.67 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.5, 165.9, 149.7, 134.3, 133.3, 131.9, 131.2, 129.0, 128.7, 128.4, 128.0, 127.9, 126.9, 125.4, 124.6, 116.7, 66.9, 42.5, 25.0, 23.4; IR (KBr) 3554, 3485, 3416, 2923, 1917, 1616, 1518, 1261, 1087, 801, 622; ESI FTMS exact mass calcd for $(C_{24}H_{21}NO_3 + H)^+$ requires *m*/*z* 372.1599, found *m*/*z* 372.1592; 93:7 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 6.460 (minor), t_R = 8.963 (major).

(S)-N-(6-Fluoro-4,4-dimethyl-2-oxo-3-phenylchroman-3-yl)-benzamide ***(3ba)***. Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 8/1; reaction time = 16 h; yield 60% (11.7 mg); white solid; mp 216−218 °C; $[\alpha]_D^{20}$ = −28.5 (*c* 0.3, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72−7.65 (m, 2H), 7.56−7.50 (m, 1H), 7.47−7.41 (m, 2H), 7.38−7.32 (m, 2H), 7.26−7.20 (m, 4H), 7.18 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.00−6.94 (m, 1H), 6.93−6.90 (m, 1H), 1.68 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.4, 165.9, 159.8 (*J* = 242), 145.5, 134.2, 133.2 (*J* = 7.0), 132.0, 128.8, 128.2, 128.0, 127.0, 118.0 (*J* = 8.4), 117.6 (*J* = 24.8), 115.4 (*J* = 23.4), 115.3, 111.8, 111.5, 66.7, 42.6, 25.3, 23.1; IR (KBr) 3526, 3270, 2965, 1772, 1516, 1483 1285, 1184, 951, 901, 815, 760; ESI FTMS exact mass calcd for $(C_{24}H_{20}FNO_3 + H)^+$ requires *m*/*z* 390.1505, found *m*/*z* 390.1496; 90:10 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 7.250 (minor), t_R = 11.647 (major).

(S)-N-(6-Chloro-4,4-dimethyl-2-oxo-3-phenylchroman-3-yl)-benzamide ***(3ca)***. Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 8/1; reaction time = 16 h; yield 95% (19.3 mg); white solid; mp 234−236 °C; $[\alpha]_D^{20}$ = −27.2 (*c* 0.3, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74−7.66 (m, 2H), 7.58−7.48 (m, 1H), 7.49−7.41 (m, 3H), 7.40−7.34 (m, 2H), 7.26−7.22 (m, 4H), 7.14 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 1.66 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.00, 166.0, 148.7, 134.0, 133.4, 132.9, 132.1, 131.9, 128.8, 128.6, 128.3, 128.2, 128.0, 127.6, 127.0, 118.4, 118.0, 66.7, 42.7, 25.0, 23.3; IR (KBr) 3551, 3479, 3412, 3071, 1772, 1668, 1616, 1519, 1282, 1230, 1085, 951, 710; ESI FTMS exact mass calcd for $(C_{24}H_{20}ClNO_3 + H)^+$ requires *m*/*z* 406.1210, found *m*/*z* 406.1207; 90:10 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 6.820 (minor), t_R = 11.367 (major).

(S)-N-(6-Bromo-4,4-dimethyl-2-oxo-3-phenylchroman-3-yl)-benzamide ***(3da)***. Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 8/1; reaction time = 16 h; yield 70% (15.7 mg); white solid; mp 227−229 °C; $[\alpha]_D^{20}$ = −45.6 (*c* 0.3, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (d, *J* = 7.6 Hz, 2H), 7.59−7.49 (m, 2H), 7.48−7.34 (m, 5H), 7.27−7.23 (m, 3H), 7.12 (s, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 1.66 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.0, 166.0, 148.7, 134.1, 133.4, 132.9, 132.1, 131.9, 128.8, 128.3, 128.2, 128.0, 127.7, 127.0, 118.4, 118.0, 66.7, 42.7, 25.1, 23.3; IR (KBr) 3386, 3273, 3069, 2923, 2853, 1772, 1667, 1518, 1484, 1076, 843, 750, 711; ESI FTMS exact mass calcd for $(C_{24}H_{20}BrNO_3 + H)^+$ requires *m*/*z* 450.0705, found *m*/*z* 450.0689; 91:9 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 6.783 (minor), t_R = 11.293 (major).

(S)-N-(4,4,6-Trimethyl-2-oxo-3-phenylchroman-3-yl)benzamidee ***(3ea)***. Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 16 h; yield 63% (12.2 mg); white solid; mp 229−231 °C; $[\alpha]_D^{20}$ = −34 (*c* 0.4, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66 (d, *J* = 7.6 Hz, 2H), 7.54−7.47 (m, 1H), 7.45−7.36 (m, 4H), 7.26−7.21 (m, 4H), 7.17 (s, 1H), 7.07 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 2.41 (s, 3H), 1.65 (s, 3H), 1.32 (s, 3H); ^{13}C

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NMR (100 MHz, $CDCl_3$) δ (ppm) 167.7, 166.0, 147.5, 135.0, 134.4, 133.4, 131.9, 130.8, 129.4, 128.7, 128.4, 127.9, 127.8, 127.0, 125.0, 116.4, 67.0, 42.4, 23.3, 25.1, 21.2; IR (KBr) 3550, 3270, 2922, 2341, 1770, 1688, 1520, 1484, 1282, 1084, 950, 813, 711; ESI FTMS exact mass calcd for $(C_{25}H_{23}NO_3 + H)^+$ requires m/z 386.1756, found m/z 386.1763; 92:8 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 5.917 (minor), t_R = 9.977 (major).

*(S)-N-(6-Ethoxy-4,4-dimethyl-2-oxo-3-phenylchroman-3-yl)-benzamide (**3fa**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 8/1; reaction time = 16 h; yield 85% (17.7 mg); white solid; mp 191−193 °C; $[\alpha]_D^{20}$ = −25.0 (c 0.3, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (d, J = 7.2 Hz, 2H), 7.55−7.48 (m, 1H), 7.45−7.34 (m, 4H), 7.25−7.17 (m, 4H), 7.00 (d, J = 2.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.80−6.71 (m, 1H), 4.07 (q, J = 7.2 Hz, 2H), 1.66 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 165.9, 156.3, 143.4, 134.4, 133.4, 132.4, 131.9, 128.7, 128.3, 128.0, 127.9, 127.0, 117.3, 113.1, 111.5, 67.0, 64.1, 42.5, 25.4, 23.1, 14.9; IR (KBr) 3657, 3349, 2976, 2933, 1768, 1667, 1518, 1493, 1423, 1308, 1198, 1046, 814, 694; ESI FTMS exact mass calcd for $(C_{26}H_{25}NO_4 + H)^+$ requires m/z 416.1862, found m/z 416.1856; 90:10 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 6.053 (minor), t_R = 7.787 (major).

*(S)-N-(6-Methoxy-4,4-dimethyl-2-oxo-3-phenylchroman-3-yl)-benzamide (**3ga**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 8/1; reaction time = 16 h; yield 65% (13.1 mg); white solid; mp 188−190 °C; $[\alpha]_D^{20}$ = −13.8 (c 0.4, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (d, J = 7.2 Hz, 2H), 7.55−7.49 (m, 1H), 7.46−7.40 (m, 2H), 7.40−7.34 (m, 2H), 7.25−7.16 (m, 4H), 6.99 (d, J = 3.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 8.8, 2.9 Hz, 1H), 3.86 (s, 3H), 1.67 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 165.9, 156.9, 143.5, 134.4, 133.3, 132.5, 131.9, 128.7, 128.3, 128.0, 127.9, 127.0, 117.4, 112.6, 110.9, 67.0, 55.7, 42.5, 25.4, 23.1; IR (KBr) 3450, 3220, 2975, 1765, 1662, 1522, 1488, 1288, 1198, 1036, 951, 815, 753; ESI FTMS exact mass calcd for $(C_{25}H_{23}NO_4 + H)^+$ requires m/z 402.1705, found m/z 402.1704; 88:12 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 7.440 (minor), t_R = 11.687 (major).

*(S)-N-(7-Fluoro-4,4-dimethyl-2-oxo-3-phenylchroman-3-yl)-benzamide (**3ha**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 8/1; reaction time = 16 h; yield 87% (16.9 mg); white solid; mp 206−208 °C; $[\alpha]_D^{20}$ = −27.7 (c 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68−7.61 (m, 2H), 7.55−7.49 (m, 1H), 7.47−7.37 (m, 5H), 7.28−7.23 (m, 3H), 7.06 (s, 1H), 7.00−6.90 (m, 1H), 6.72 (dd, J = 8.8, 2.6 Hz, 1H), 1.63 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.9, 165.9, 162.4 (J = 247), 150.4 (J = 11.6), 134.0, 133.0, 132.1, 128.8, 128.4, 128.2, 127.9, 126.9, 125.7 (J = 9.2), 112.1 (J = 21.2), 104.7 (J = 25.4), 66.8, 42.3, 24.9, 23.7; IR (KBr) 3481, 3332, 3051, 2923, 1787, 1646, 1486, 1544, 1163, 950, 816, 751; ESI FTMS exact mass calcd for $(C_{24}H_{20}FNO_3 + H)^+$ requires m/z 390.1505, found m/z 390.1503; 90:10 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 6.643 (minor), t_R = 10.277 (major).

*N-((3S,4R)-4-Ethyl-4-methyl-2-oxo-3-phenylchroman-3-yl)-benzamide (**3ia**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 48 h; yield 43% (8.3 mg); >95:5 dr; white solid; mp 168−170 °C; $[\alpha]_D^{20}$ = −50 (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (d, J = 6.8 Hz, 2H), 7.47−7.42 (m, 1H), 7.42−7.33 (m, 4H), 7.32−7.28 (m, 4H), 7.26−7.19 (m, 2H), 7.07 (dd, J = 8.0, 1.0 Hz, 1H), 6.31 (s, 1H), 1.90−1.80 (m, 1H), 1.79−1.69 (m, 1H), 1.15 (s, 3H), 0.68 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.7, 164.5, 150.7, 133.6, 133.0, 132.0, 129.5, 129.2, 128.7, 128.0, 127.5, 127.4, 127.3, 126.7, 124.2, 116.8, 66.7, 47.0, 28.0, 16.7, 8.8; IR (KBr) 3513, 3272, 2969, 1787, 1667, 1580, 1513, 1485, 1284, 1223, 1125, 1088, 799, 747, 701; ESI FTMS exact mass calcd for $(C_{25}H_{23}NO_3 + H)^+$ requires m/z 386.1756, found m/z 386.1751; 91:9 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 12.463 (minor), t_R = 13.640 (major).

*N-((3S,4R)-4-Ethyl-4-methyl-2-oxo-3-phenylchroman-3-yl)-4-methylbenzamide (**3ja**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; yield 42% (8.4 mg); >95:5 dr; white solid; mp 172−173 °C; $[\alpha]_D^{20}$ = −17.0 (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (d, J = 6.8 Hz, 2H), 7.42−7.33 (m, 4H), 7.33−7.28 (m, 1H), 7.25−7.17 (m, 3H), 7.13−7.07 (m, 2H), 7.07−7.02 (m, 1H), 6.30 (s, 1H), 2.33 (s, 3H), 1.88−1.79 (m, 1H), 1.78−1.68 (m, 1H), 1.15 (s, 3H), 0.67 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.6, 164.6, 150.7, 142.5, 133.1, 130.7, 129.4, 129.3, 129.2, 127.9, 127.4, 127.3, 126.7, 124.2, 116.7, 66.7, 47.0, 28.0, 21.5, 16.7, 8.8; IR (KBr) 3400, 2934, 1789, 1661, 1613, 1524, 1471, 1282, 1230, 1129, 1092, 946, 755, 748; ESI FTMS exact mass calcd for $(C_{26}H_{25}NO_3 + H)^+$ requires m/z 400.1913, found m/z 400.1910; 85:15 er, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 85/15, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 19.080 (minor), t_R = 23.283 (major).

*(S)-N-(3-(4-Chlorophenyl)-4,4-dimethyl-2-oxochroman-3-yl)-benzamide (**3ab**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 16 h; yield 99% (20.1 mg); white solid; mp 215−217 °C; $[\alpha]_D^{20}$ = −15.8 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (d, J = 7.2 Hz, 2H), 7.88−7.83 (m, 1H), 7.81−7.74 (m, 3H), 7.70−7.65 (m, 3H), 7.64−7.61 (m, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.41 (s, 1H), 7.32 (dd, J = 8.0, 1.3 Hz, 1H), 1.96 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.0, 165.9, 149.6, 134.1, 132.1, 131.9, 129.8, 129.2, 128.8, 128.1, 126.9, 125.6, 124.6, 116.8, 66.6, 42.5, 24.7, 23.4; IR (KBr) 3633, 3304, 2977, 1919, 1773, 1648, 1579, 1486, 1286, 1083, 947, 750, 689; ESI FTMS exact mass calcd for $(C_{24}H_{20}ClNO_3 + H)^+$ requires m/z 406.1210, found m/z 406.1209; 91:9 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 7.040 (minor), t_R = 12.497 (major).

*(S)-N-(3-(3-Chlorophenyl)-4,4-dimethyl-2-oxochroman-3-yl)-benzamide (**3ac**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 16 h; yield 72% (14.6 mg); white solid; mp 230−232 °C; $[\alpha]_D^{20}$ = −11.9 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) δ 7.56 (d, J = 7.2 Hz, 2H), 7.54−7.49 (m, 1H), 7.45 (dd, J = 7.6, 1.7 Hz, 1H), 7.42−7.38 (m, 3H), 7.35−7.29 (m, 2H), 7.29−7.27 (m, 1H), 7.26−7.23 (m, 1H), 7.22−7.16 (m, 1H), 7.03−6.90 (m, 2H), 1.61 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.5, 166.0, 149.7, 135.4, 133.9, 133.9, 132.1, 130.6, 129.3, 129.0, 128.8, 128.7, 128.3, 126.9, 126.8, 125.5, 124.7, 116.8, 66.5, 42.7, 24.2, 23.7; IR (KBr) 3442, 2974, 1777, 1646, 1586, 1515, 1447, 1411, 1284, 1195, 1129, 1080, 959, 787, 695; ESI FTMS exact mass calcd for $(C_{24}H_{20}ClNO_3 + H)^+$ requires m/z 406.1210, found m/z 406.1200; 90:10 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 6.440 (minor), t_R = 8.420 (major).

*(S)-N-(4,4-Dimethyl-2-oxo-3-phenylchroman-3-yl)-4-ethoxybenzamide (**3ad**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 16 h; yield 72% (14.9 mg); white solid; mp 164−166 °C; $[\alpha]_D^{20}$ = −38.8 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57 (d, J = 8.4 Hz, 2H), 7.45 (dd, J = 7.2, 1.8 Hz, 1H), 7.42−7.35 (m, 2H), 7.32−7.27 (m, 1H), 7.26−7.20 (m, 4H), 6.99 (s, 1H), 6.95 (dd, J = 7.8, 1.5 Hz, 1H), 6.91−6.83 (m, 2H), 4.06 (d, J = 7.2 Hz, 2H), 1.64 (s, 3H), 1.42 (t, J = 6.8 Hz, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.5, 165.5, 161.9, 149.8, 133.4, 131.2, 129.0, 128.8, 128.4, 127.9, 127.8, 126.3, 125.3, 124.6, 116.7, 114.4, 66.8, 63.7, 42.5, 24.7, 23.5, 14.7; IR (KBr) 3526, 3269, 2923, 1759, 1488, 1287, 1252, 950, 764, 762; ESI FTMS exact mass calcd for $(C_{26}H_{25}NO_4 + H)^+$ requires m/z 416.1862, found m/z 416.1862; 95:5 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol =

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70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 10.283 (minor), t_R = 24.557 (major).

*(S)-N-(4,4-Dimethyl-2-oxo-3-phenylchroman-3-yl)-4-methoxybenzamide (**3ae**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 16 h; yield 67% (13.4 mg); white solid; mp 168−170 °C; $[\alpha]_D^{20}$ = −4.0 (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (d, J = 8.8 Hz, 2H), 7.45 (dd, J = 7.6, 1.8 Hz, 1H), 7.41−7.36 (m, 2H), 7.31−7.26 (m, 1H), 7.25−7.21 (m, 4H), 6.99 (s, 1H), 6.95 (dd, J = 8.0, 1.5 Hz, 1H), 6.92−6.86 (m, 2H), 3.84 (s, 3H), 1.64 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.4, 162.5, 149.8, 133.4, 129.0, 128.8, 128.4, 127.9, 127.8, 126.5, 125.3, 124.6, 116.7, 113.9, 66.8, 55.5, 42.5, 24.8, 23.5; IR (KBr) 3525, 3270, 2966, 1783, 1661, 1604, 1447, 1255, 1084, 1019, 842, 752, 702; ESI FTMS exact mass calcd for $(C_{25}H_{23}NO_4 + H)^+$ requires m/z 402.1705, found m/z 402.1702; 94:6 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 10.127 (minor), t_R = 20.970 (major).

*(S)-N-(4,4-Dimethyl-2-oxo-3-phenylchroman-3-yl)-3-methoxybenzamide (**3af**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 16 h; yield 99% (20.0 mg); white solid; mp 187−189 °C; $[\alpha]_D^{20}$ = −11.3 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.47−7.43 (m, 1H), 7.42−7.36 (m, 2H), 7.33−7.26 (m, 3H), 7.26−7.17 (m, 4H), 7.12 (d, J = 7.6 Hz, 1H), 7.08 (s, 1H), 7.06−7.01 (m, 1H), 6.99−6.94 (m, 1H), 3.78 (s, 3H), 1.65 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.3, 165.8, 159.9, 149.7, 135.7, 133.2, 131.1, 129.7, 129.0, 128.4, 128.0, 127.8, 125.4, 124.6, 118.4, 118.4, 116.7, 112.2, 66.9, 55.4, 42.6, 24.7, 23.5; IR (KBr) 3351, 3059, 2961, 1781, 1658, 1581, 1484, 1449, 1283, 1083, 1041, 949, 772; ESI FTMS exact mass calcd for $(C_{25}H_{23}NO_4 + H)^+$ requires m/z 402.1705, found m/z 402.1707; 93:7 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol =70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 6.557 (minor), t_R = 7.980 (major).

*(S)-N-(4,4-Dimethyl-2-oxo-3-phenylchroman-3-yl)-4-methylbenzamide (**3ag**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 16 h; yield 93% (17.9 mg); white solid; mp 181−183 °C; $[\alpha]_D^{20}$ = −21.1 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.51 (d, J = 8.0 Hz, 2H), 7.47−7.43 (m, 1H), 7.42−7.36 (m, 2H), 7.31−7.18 (m, 7H), 7.05 (s, 1H), 6.98−6.93 (m, 1H), 2.38 (s, 3H), 1.64 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.4, 165.9, 149.7, 142.5, 133.4, 131.4, 131.2, 129.4, 129.0, 128.4, 128.0, 127.8, 126.9, 125.3, 124.6, 116.7, 66.8, 42.6, 24.7, 23.5, 21.5; IR (KBr) 3650, 3529, 2919, 1784, 1741, 1658, 1523, 1449, 1285, 1129, 1084, 949, 833; ESI FTMS exact mass calcd for $(C_{25}H_{23}NO_3 + H)^+$ requires m/z 386.1756, found m/z 386.1750; 96:4 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 8.510 (minor), t_R = 15.013 (major).

*(S)-4-Bromo-N-(4,4-dimethyl-2-oxo-3-phenylchroman-3-yl)-benzamide (**3ah**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 16 h; yield 63% (14.1 mg); white solid; mp 147−149 °C; $[\alpha]_D^{20}$ = −17.1 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57−7.43 (m, 5H), 7.37−7.31 (m, 2H), 7.30−7.27 (m, 1H), 7.26−7.19 (m, 4H), 7.12 (s, 1H), 6.95 (dd, J = 7.6, 1.5 Hz, 1H), 1.67 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.5, 165.0, 149.6, 133.1, 132.0, 131.1, 129.0, 128.5, 128.3, 128.1, 127.9, 126.7, 125.5, 124.6, 116.7, 67.1, 42.5, 25.2, 23.2; IR (KBr) 3526, 3267, 2924, 1782, 1651, 1524, 1482, 1447, 1224, 1008, 950, 753, 702; ESI FTMS exact mass calcd for $(C_{24}H_{20}BrNO_3 + H)^+$ requires m/z 450.0705, found m/z 450.0679; 87:13 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 75/25, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 9.640 (minor), t_R = 16.097 (major).

*(S)-3-Bromo-N-(4,4-dimethyl-2-oxo-3-phenylchroman-3-yl)-benzamide (**3ai**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 4/1; reaction time = 16 h; yield 67% (15.1 mg); white solid; mp 213−215 °C; $[\alpha]_D^{20}$ = −41.8 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75 (s, 1H), 7.66−7.62 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.49−7.48 (m, 1H), 7.37−7.32 (m, 2H), 7.32−7.26 (m, 3H), 7.25−7.21 (m, 3H), 7.15 (s, 1H), 6.99−6.93 (m, 1H), 1.69 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.6, 164.6, 149.5, 136.3, 134.9, 133.0, 131.1, 130.3, 130.3, 129.1, 128.3, 128.1, 128.0, 125.5, 125.3, 124.5, 123.0, 116.7, 67.1, 42.5, 25.4, 23.1; IR (KBr) 3552, 3477, 3412, 2929, 1778, 1616, 1510, 1229, 1130, 1083, 950, 885, 746; ESI FTMS exact mass calcd for $(C_{24}H_{20}BrNO_3 + H)^+$ requires m/z 450.0705, found m/z 450.0671; 90:10 er, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 7.503 (minor), t_R = 8.303 (major).

Synthetic Procedure and Characterization Data of Compound 11. Compound **3aa** (0.1 mmol) was dissolved in propylamine (1 mL) and the reaction mixture was stirred at room temperature for 3 h. After the completion of the reaction, the reaction mixture was directly purified by flash chromatography to afford pure product **11**.

*(R)-N-(3-(2-Hydroxyphenyl)-3-methyl-1-oxo-2-phenyl-1-(propylamino)butan-2-yl)benzamide (**11**).* Flash column chromatography eluent (flushed by 10% Et_3N/petroleum ether in advance), petroleum ether/ethyl acetate = 2/1; reaction time = 3 h; yield 99% (42.6 mg); white solid; mp 222−223 °C; $[\alpha]_D^{20}$ = −14.0 (c 0.2, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.98 (s, 1H), 7.89−7.81 (m, 2H), 7.77 (s, 1H), 7.46−7.36 (m, 1H), 7.34−7.26 (m, 2H), 7.22−7.15 (m, 3H), 7.10 (s, 1H), 7.02−6.95 (m, 1H), 6.76−6.69 (m, 2H), 6.64 (s, 1H), 3.04−2.93 (m, 1H), 2.89−2.78 (m, 1H), 1.66 (s, 3H), 1.53 (s, 3H), 1.23−1.11 (m, 2H), 0.64 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.4, 168.1, 154.9, 137.3, 134.2, 132.0, 131.3, 130.7, 128.9, 128.8, 128.5, 127.4, 126.9, 126.9, 126.8, 119.8, 117.9, 73.3, 46.2, 41.6, 27.2, 26.4, 22.0, 11.4; IR (KBr) 3320, 2971, 2932, 2875, 1750, 1540, 1444, 1375, 1294, 1155, 703; ESI FTMS exact mass calcd for $(C_{27}H_{30}N_2O_3 + H)^+$ requires m/z 431.2335, found m/z 431.2330; 99:1 er, determined by HPLC (Daicel Chiralpak IC, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 5.560 (minor), t_R = 26.300 (major).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00078.

Screening of catalysts and condition optimization, characterization data (including ^{1}H and ^{13}C NMR and HPLC spectra) for products **3** and **11**, ^{1}H NMR study on the interaction between catalysts **5** and **6**, NOE spectrum of product **3ja**, and single-crystal data of product **3aa** (PDF)

Single-crystal data of product **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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