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Tandem intramolecular oxa-Michael addition/decarboxylation reaction catalyzed by bifunctional cinchona alkaloids: facile synthesis of chiral flavanone derivatives

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ABSTRACT

Bifunctional cinchona alkaloids were used to catalyze a tandem intramolecular oxa-Michael addition/decarboxylation reaction of alkylidene β-ketoesters **1**, providing a series of flavanone derivatives with up to 97% yield and 93% ee.

1. Introduction

Together with the rapid development of organocatalysis in recent years, the organocatalytic asymmetric Michael-type reaction, including Michael and hetero-Michael reaction, has emerged as an efficient tool for accessing many useful molecules.[1] Cinchona alkaloids, which are easily available and well-documented powerful bifunctional organocatalysts in many other reactions,[2] have also found extensive applications in the asymmetric Michael reaction.[3] Whereas there are numerous examples of hetero-Michael addition with thiols[4] as non-carbon nucleophiles catalyzed by cinchona alkaloids, the aza-Michael,[5] and oxa-Michael[6] reactions are less studied.

Recently, significant advances have been made in the synthesis of biologically interesting flavanones via a catalytic asymmetric intramolecular oxa-Michael reaction of alkylidene β-ketoesters **1**. Scheidt and co-workers pioneered the use of **1** as the advantageous substrates for this transformation and obtained excellent results using cinchona derived thiourea catalysts.[7] Our group also developed an organocatalytic tandem intramolecular oxa-Michael addition/electrophilic fluorination reaction of **1** to afford fluorinated flavanones **5** (Scheme 1, Eq. a).[8] In our study, we found that bifunctional cinchona alkaloids **3** (Fig. 1) are efficient catalysts for this reaction. Herein, we reported the application of the catalysts **3** to a similar tandem intramolecular oxa-Michael addition/decarboxylation reaction of alkylidene β-ketoesters **1**, which provided flavanone derivatives **2** in excellent yields and moderate to high enantioselectivities (Scheme 1, Eq. b).

2. Results and discussion

As a model substrate, α,β-unsaturated ketone **1a** was first studied in the tandem reaction in the presence of various cinchona alkaloids to afford the product **2a** (Table 1). The structures of the catalysts proved to be highly influential on both the reaction rate and enantioselectivity. First, commercially available quinine (**3a**) and quinidine (**3b**) were used and the desired product **2a** was obtained with low enantiomeric excesses (ee) after a long reaction time (Table 1, entries 1 and 2). When the corresponding 6-hydroxy catalysts **3c** and **3d** were used, only a little higher ee was obtained (Table 1, entries 3 and 4). Different from the result from our previously developed tandem intramolecular oxa-Michael addition/electrophilic fluorination reaction of **1**, the quinidine-derived catalyst **3i**, instead of **3l**, was identified as the best one in light of both catalytic activity and enantioselectivity (Table 1, entry 9). It is also of note that either the quinine-derived **3e** (Table 1, entry 5) or other sterically more demanding catalysts, such as **3f**–**h**, **3j**–**m**, provided inferior results (Table 1, entries 6–8 and 10–13).

With the identified optimal catalyst **3i**, other reaction conditions, such as catalyst loading, solvents, and substrate concentration were

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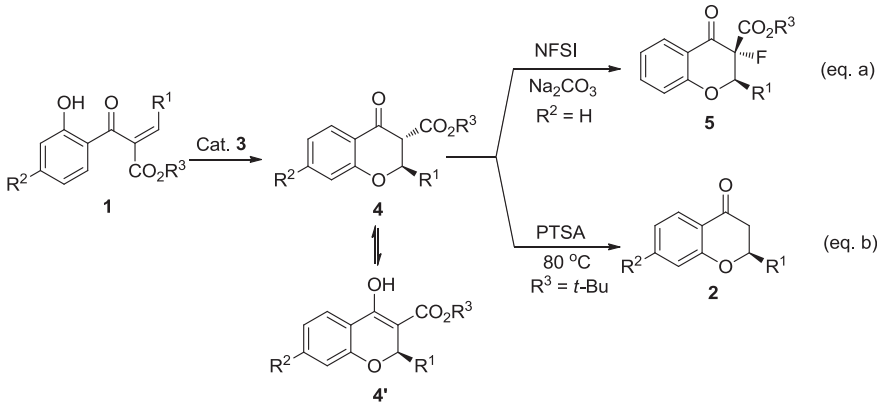


Scheme 1. Synthesis of fluorinated flavanone derivatives **5** and flavanone derivatives **2** using bifunctional cinchona alkaloid catalysts.

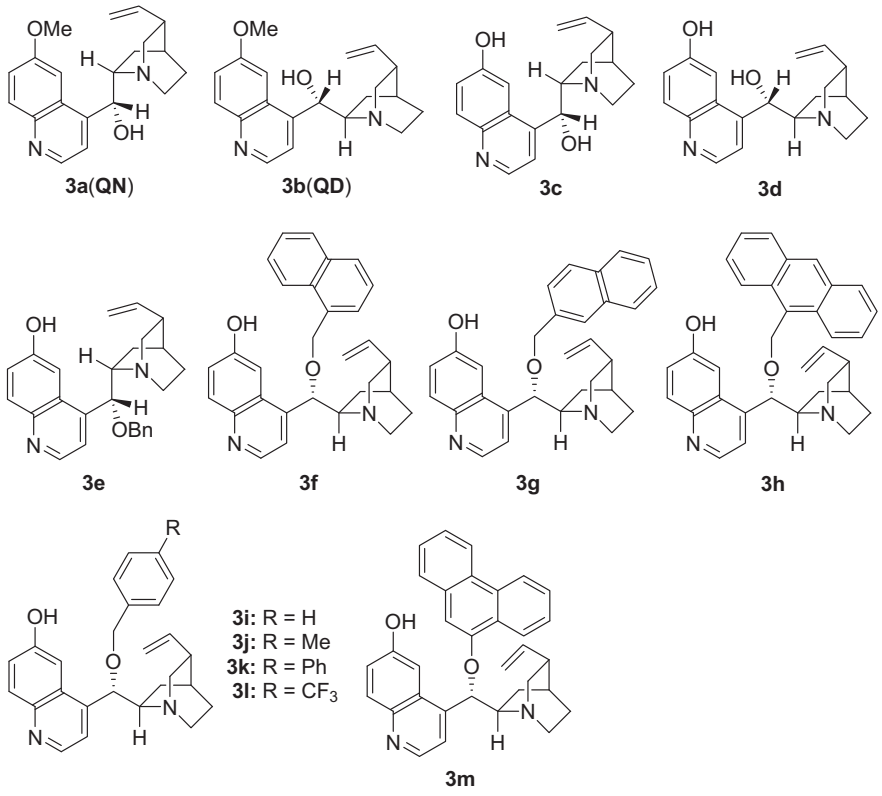
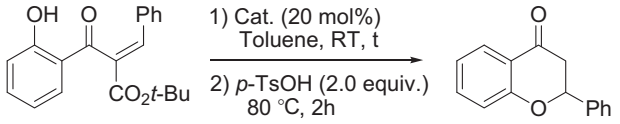


Fig. 1. Cinchona alkaloids used in this study.

next examined (Table 2). Decreasing the catalyst loading from 20 to 15, 10 or 5 mol % led to a drop in both the yield and enantioselectivity, together with significantly longer reaction times (Table 2, entries 1–4). Among the solvents screened, $PhCF_3$ gave the highest ee value (up to 90%), albeit with a slightly lower yield (Table 2, entries 6). Variation of the amount of the reaction solvent $PhCF_3$ revealed a slight influence on the reaction results: increasing the concentration from 0.1 to 0.2 M or 0.5 M, a drop in the ee value was observed (Table 2, entries 6 and 12–13), whereas slightly higher ee value and yield were obtained at a lower concentration of 0.05 M at the expense of a much longer reaction time (Table 2, entry 14). To summarize, the present tandem reaction was best performed with 20 mol % of **3i** in $PhCF_3$ (0.1 M) at room temperature, followed by treatment with PTSA (2 equiv) at 80 °C for 2 h.

With the optimal conditions for the intramolecular Michael addition/decarboxylation cascade reaction at hand, we then explored the scope of the reaction and the results were listed in Table 3. Of all the substrates examined, excellent yields were generally obtained. For substrates **1a**–**g** where R^1 are differently substituted benzene rings, relatively shorter reaction times were needed for substrates with electron-withdrawing groups while no consistent trend in the enantioselectivity was observed (Table 3, entries 1–7). When R^1 are bulkier naphthyl groups (**1h** and **1i**), longer reaction times and apparently lower ee values were observed (Table 3, entries 8 and 9). Pleasingly, substrate **1j** bearing an alkyl R^1 (R^1=cyclohexyl) also participated in the reaction well to afford the desired product with high enantioselectivity (up to 90% ee), although a long reaction time was required (Table 3, entry 10). Changing the R^2 group of substrate **1a** to an electron-donating methyl or methoxyl group resulted in somewhat diminished ee values as well as prolonged reaction times (Table 3, entries 1 and 11–12).

Table 1
Evaluation of different cinchona alkaloids as catalysts in the asymmetric intramolecular oxa-Michael addition[a]

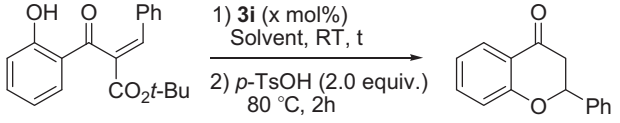


1a 2a

Entry	Catalyst	*t*	Yield[b] (%)	ee[c] (%)
1	**3a**(QN)	13 days	85	−26
2	**3b** (QD)	9 days	98	16
3	**3c**	13 days	80	−36
4	**3d**	13 days	89	24
5	**3e**	7 days	98	−88
6	**3f**	24 h	96	84
7	**3g**	24 h	>99	82
8	**3h**	7 days	89	76
9	**3i**	24 h	>99	87
10	**3j**	36 h	95	86
11	**3k**	24 h	98	85
12	**3l**	16 h	96	86
13	**3m**	12 days	71	39

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.1 mmol), catalyst **3** (0.02 mmol), and toluene (1.0 mL) at room temperature, then *p*-TsOH (0.2 mmol) was added at 80 °C for 2 h.
[b] Yield of the isolated product after column chromatography on silica gel.
[c] Determined by HPLC analysis on a chiral column.

Table 2
Optimization of reaction conditions with catalyst **3i**[a]

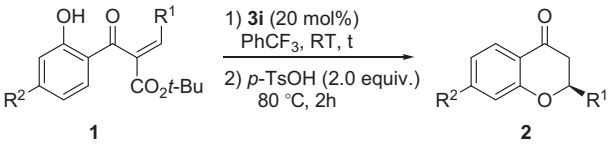


1a 2a

Entry	**3i** (mol %)	Solvent	*t* (h)	Yield[b] (%)	ee[c] (%)
1	20	Toluene	24	>99	87
2	15	Toluene	36	98	85
3	10	Toluene	48	98	80
4	5	Toluene	48	92	79
5	20	Xylene	24	96	85
6	20	$PhCF_3$	24	92	90
7	20	$ClCH_2CH_2Cl$	12	85	76
8	20	$CHCl_3$	12	96	74
9	20	CCl_4	24	98	83
10	20	CH_3CN	24	85	69
11	20	PhOMe	24	>99	85
12[d]	20	$PhCF_3$	16	91	80
13[e]	20	$PhCF_3$	16	94	83
14[f]	20	$PhCF_3$	84	96	91

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.1 mmol) and **3i** in solvent (1.0 mL) at room temperature for 12–84 h, then *p*-TsOH (0.2 mmol) was added at 80 °C for 2 h.
[b] Yield of the isolated product after column chromatography on silica gel.
[c] Determined by HPLC analysis on a chiral column.
[d] $PhCF_3$ (0.2 mL) was used.
[e] $PhCF_3$ (0.5 mL) was used.
[f] $PhCF_3$ (2.0 mL) was used.

Table 3
Examination of the reaction scope[a]



1 2

Entry	R^1, R^2, **1**	*t* (h)	Product	Yield[b] (%)	ee[c] (%)
1	C_6H_5, H, **1a**	24	**2a**	92	90
2	*p*-BrC_6H_4, H, **1b**	16	**2b**	88	86
3	*p*-CNC_6H_4, H, **1c**	16	**2c**	97	88
4	*p*-PhC_6H_4, H, **1d**	24	**2d**	82	71
5	*p*-MeC_6H_4, H, **1e**	36	**2e**	85	61
6	*o*-ClC_6H_4, H, **1f**	18	**2f**	95	78
7	*m*-MeC_6H_4, H, **1g**	36	**2g**	85	79
8	1-Naphthyl, H, **1h**	48	**2h**	88	72
9	2-Naphthyl, H, **1i**	48	**2i**	80	60
10	Cyclohexyl, H, **1j**	120	**2j**	97	90
11	C_6H_5, Me, **1k**	48	**2k**	89	83
12	C_6H_5, MeO, **1l**	48	**2l**	93	82

[a] Unless otherwise noted, the reaction was carried out with **1** (0.1 mmol), **3i** (0.02 mmol), and $PhCF_3$ (1.0 mL) at room temperature for 16–120 h, then *p*-TsOH (0.2 mmol) was added at 80 °C for 2 h.
[b] Yield of the isolated product after column chromatography on silica gel.
[c] Determined by HPLC analysis on a chiral column. The absolute configuration of product **2** was determined as *S* by comparison of optical rotation values to literature data.[7,9]

As an extension of our current efforts on the utilization of **1** to synthesize flavanones with varied functionalities, instead of the treatment with PTSA, several electrophiles were introduced into the system for an ensuing electrophilic cascade reaction after intramolecular Michael addition (Scheme 2). To our delight, the use of methyl vinyl ketone (MVK), *N*-bromosuccinimide (NBS), and *N*-chlorosuccinimide (NCS) all smoothly led to the desired flavanone derivatives **6**–**8** in high to excellent yields and 92–93% ee values under mild conditions.

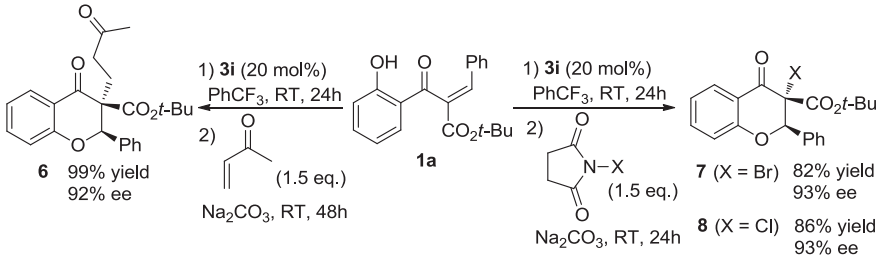
3. Conclusion

In summary, we have developed an intramolecular oxa-Michael addition/decarboxylation or electrophilic cascade reaction of alkylidene β-ketoesters catalyzed by bifunctional cinchona alkaloids, which provides an easy access to a series of chiral flavanone derivatives. High enantioselectivities (up to 93% ee) and excellent yields were obtained by using quinidine-derived catalyst **3i**. Further efforts toward the application of the bifunctional cinchona alkaloids catalysts in other reactions are in progress in our laboratories.

4. Experimental

4.1. General

Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers and purified by standard



Scheme 2. Organocatalytic intramolecular oxa-Michael addition/electrophilic halogenation cascade reaction.

techniques. Flash column chromatography was performed using silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a DPX-300 or Varian EM-360 (300 MHz) and DPX-400 (100 MHz) with TMS as the internal standard. ^{19}F NMR spectra were recorded at 282 MHz with $CFCl_3$ as the external standard. All chemical shifts (δ) are given in parts per million. Data are reported as follows: chemical shift, multiplicity (s=single, d=doublet, t=triplet, q=quartet, br=broad, and m=multiplet) and coupling constants (Hz), integration. Analytical high-performance liquid chromatography (HPLC) was carried out on WATERS equipment using a chiral column. Melting points were determined on an SGW X-4 apparatus, and are uncorrected. Optical rotations were measured on a JASCO P-1030 Polarimeter at λ=589 nm. IR spectra were recorded on a Perkin–Elmer 983G instrument. Elementary analysis was taken on a Vario EL III elementary analysis instrument. Mass spectra analysis was performed on API 200 LC/MS system (Applied Biosystems Co. Ltd).

Catalysts **3a**–**m** were prepared according to the procedure of Zhao[8] and references therein.

Substrates **1a**–**l** were prepared according to the procedure of Scheidt[7] and Feng.[9]

4.2. General procedure for cyclization/decarboxylation reaction

A mixture of (*E*)-*tert*-butyl 2-(2-hydroxybenzoyl)-3-phenylacrylate **1** (0.1 mmol) and catalyst **3i** (8 mg, 0.02 mmol) in 1.0 mL of $PhCF_3$ was stirred at room temperature for the appropriate times until the disappearance of **1** (monitored by TLC). Then *p*-toluenesulfonic acid (*p*-TsOH) (38 mg, 0.2 mmol) was added and the mixture was stirred at 80 °C for 2 h (monitored by TLC). The reaction mixture was then concentrated, and the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether=1/20) to give the desired products **2**.

*4.2.1. (S)-2-Phenylchroman-4-one (**2a**)*[7]. White solid (20.5 mg, 92% isolated yield, 90% ee). $[\alpha]_D^{23}$ −54.9 (*c* 0.20, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (dd, J_1=2.7 Hz, J_2=16.8 Hz, 1H), 3.11 (dd, J_1=13.2 Hz, J_2=16.8 Hz, 1H), 5.50 (dd, J_1=2.1 Hz, J_2=13.2 Hz, 1H), 7.05–7.08 (m, 2H), 7.37–7.55 (m, 6H), 7.94 (d, J=7.5 Hz, 1H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 90/10, flow rate: 1.0 mL/min, t_r (minor)=8.19 min, t_r (major)=10.11 min.

*4.2.2. (S)-2-(4-Bromophenyl)chroman-4-one (**2b**)*[7]. White solid (26.6 mg, 88% isolated yield, 86% ee). $[\alpha]_D^{24}$ −47.8 (*c* 0.26, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (dd, J_1=2.4 Hz, J_2=16.8 Hz, 1H), 3.03 (dd, J_1=12.9 Hz, J_2=16.8 Hz, 1H), 5.50 (dd, J_1=2.1 Hz, J_2=12.9 Hz, 1H), 7.04–7.09 (m, 2H), 7.37 (d, J=8.1 Hz, 2H), 7.50–7.58 (m, 3H), 7.93 (d, J=8.1 Hz, 1H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 90/10, flow rate: 1.0 mL/min, t_r (minor)=9.58 min, t_r (major)=12.53 min.

*4.2.3. (S)-4-(4-Oxochroman-2-yl)benzonitrile (**2c**)*[9]. White solid (24.2 mg, 97% isolated yield, 88% ee). $[\alpha]_D^{24}$ −75.6 (*c* 0.24, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90–3.06 (m, 2H), 5.56 (d, J=10.8 Hz, 1H), 7.08 (d, J=6.6 Hz, 2H), 7.54–7.73 (m, 5H), 7.94 (d, J=6.0 Hz, 1H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 90/10, flow rate: 1.0 mL/min, t_r (minor)=21.32 min, t_r (major)=25.52 min.

*4.2.4. (S)-2-(Biphenyl-4-yl)chroman-4-one (**2d**)*[9]. White solid (24.7 mg, 82% isolated yield, 71% ee). $[\alpha]_D^{24}$ −35.3 (*c* 0.24, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (d, J=16.2 Hz, 1H), 3.13 (dd, J_1=12.3 Hz, J_2=16.2 Hz, 1H), 5.52 (d, J=12.3 Hz, 1H), 7.07 (d, J=6.0 Hz, 2H), 7.24–7.64 (m, 10H), 7.95 (d, J=6.3 Hz, 1H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 95/5, flow rate: 1.0 mL/min, t_r (minor)=18.29 min, t_r (major)=19.72 min.

*4.2.5. (S)-2-p-Tolylchroman-4-one (**2e**)*[7]. Colorless liquid (20.3 mg, 85% isolated yield, 61% ee). $[\alpha]_D^{25}$ −26.4 (*c* 0.19, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.87 (d, J=16.5 Hz, 1H), 3.10 (dd, J_1=12.9 Hz, J_2=16.5 Hz, 1H), 5.45 (d, J=12.9 Hz, 1H), 7.04 (d, J=7.2 Hz, 2H), 7.24 (d, J=6.9 Hz, 2H), 7.38 (d, J=6.9 Hz, 2H), 7.50 (t, J=7.2 Hz, 1H), 7.93 (d, J=7.2 Hz, 1H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 90/10, flow rate: 1.0 mL/min, t_r (minor)=7.54 min, t_r (major)=8.71 min.

*4.2.6. (S)-2-(2-Chlorophenyl)chroman-4-one (**2f**)*[7]. Yellow solid (24.7 mg, 95% isolated yield, 78% ee). $[\alpha]_D^{25}$ −135.0 (*c* 0.24, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87–3.07 (m, 2H), 5.88 (d, J=11.7 Hz, 1H), 7.06–7.11 (m, 2H), 7.30–7.43 (m, 3H), 7.53 (t, J=7.5 Hz, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.96 (d, J=7.5 Hz, 1H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 90/10, flow rate: 1.0 mL/min, t_r (minor)=6.31 min, t_r (major)=6.74 min.

*4.2.7. (S)-2-m-Tolylchroman-4-one (**2g**)*[9]. Colorless liquid (20.2 mg, 85% isolated yield, 79% ee). $[\alpha]_D^{25}$ −49.0 (*c* 0.19, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.87 (dd, J_1=2.7 Hz, J_2=16.8 Hz, 1H), 3.10 (dd, J_1=13.8 Hz, J_2=16.8 Hz, 1H), 5.50 (dd, J_1=2.7 Hz, J_2=13.8 Hz, 1H), 7.03–7.07 (m, 2H), 7.20 (d, J_2=7.2 Hz, 1H), 7.25–7.35 (m, 3H), 7.51 (t, J_2=7.5 Hz, 1H), 7.94 (d, J=8.1 Hz, 1H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 90/10, flow rate: 1.0 mL/min, t_r (minor)=7.15 min, t_r (major)=9.00 min.

*4.2.8. (S)-2-(Naphthalen-1-yl)chroman-4-one (**2h**)*[9]. White solid (24.0 mg, 88% isolated yield, 72% ee). $[\alpha]_D^{23}$ −31.5 (*c* 0.23, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (d, J=16.5 Hz, 1H), 3.26 (dd, J_1=12.3 Hz, J_2=16.5 Hz, 1H), 6.23 (d, J=12.3 Hz, 1H), 7.09 (d, J=6.9 Hz, 2H), 7.40–7.64 (m, 4H), 7.78 (d, J=6.9 Hz, 1H), 7.87–7.91 (m, 2H), 7.99–8.06 (m, 2H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 80/20, flow rate: 1.0 mL/min, t_r (minor)=11.11 min, t_r (major)=15.69 min.

*4.2.9. (S)-2-(Naphthalen-2-yl)chroman-4-one (**2i**)*[7]. White solid (21.9 mg, 80% isolated yield, 60% ee). $[\alpha]_D^{24}$ −45.6 (*c* 0.19, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (d, J=15.9 Hz, 1H), 3.18 (dd, J_1=12.9 Hz, J_2=15.9 Hz, 1H), 5.64 (d, J=12.9 Hz, 1H), 7.04–7.10 (m, 2H), 7.50–7.60 (m, 4H), 7.86–7.97 (m, 5H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 80/20, flow rate: 1.0 mL/min, t_r (minor)=10.84 min, t_r (major)=17.60 min.

*4.2.10. (S)-2-Cyclohexylchroman-4-one (**2j**)*[7]. Colorless liquid (22.3 mg, 97% isolated yield, 90% ee). $[\alpha]_D^{23}$ +58.9 (*c* 0.23, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07–1.33 (m, 5H), 1.67–1.83 (m, 5H), 1.99 (d, J=12.3 Hz, 1H), 2.61–2.78 (m, 2H), 4.16–4.24 (m, 1H), 6.96–7.01 (m, 2H), 7.46 (t, J=7.5 Hz, 1H), 7.86 (d, J=7.5 Hz, 1H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 100/1, flow rate: 1.0 mL/min, t_r (minor)=7.27 min, t_r (major)=7.73 min.

*4.2.11. (S)-7-Methyl-2-phenylchroman-4-one (**2k**)*[7]. White waxy solid (21.2 mg, 89% isolated yield, 83% ee). $[\alpha]_D^{23}$ −61.6 (*c* 0.20, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.86 (dd, J_1=3.0 Hz, J_2=17.1 Hz, 1H), 3.05 (dd, J_1=13.2 Hz, J_2=16.8 Hz, 1H), 5.46 (dd, J_1=2.7 Hz, J_2=13.2 Hz, 1H), 6.86–6.88 (m, 2H), 7.37–7.49 (m, 5H), 7.82 (d, J=8.1 Hz, 1H). The ee was determined by HPLC analysis

using a chiralcel OD-H column, hexane/2-propanol: 90/10, flow rate: 1.0 mL/min, t_r (minor)=7.62 min, t_r (major)=10.55 min.

*4.2.12. (S)-7-Methoxy-2-phenylchroman-4-one (**2l**)*[7]. Colorless liquid (23.5 mg, 93% isolated yield, 82% ee). $[\alpha]_D^{23}$ −70.4 (*c* 0.23, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (dd, J_1=2.4 Hz, J_2=16.5 Hz, 1H), 3.05 (dd, J_1=13.2 Hz, J_2=16.5 Hz, 1H), 5.47 (dd, J_1=2.4 Hz, J_2=13.2 Hz, 1H), 6.50 (d, J=1.8 Hz, 1H), 6.62 (dd, J_1=2.1 Hz, J_2=8.7 Hz, 1H), 7.36–7.49 (m, 5H), 7.87 (d, J=9.0 Hz, 1H). The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 90/10, flow rate: 1.0 mL/min, t_r (minor)=9.90 min, t_r (major)=12.83 min.

4.3. General procedure for cyclization/electrophilic cascade reaction to obtain products 6, 7, and 8

A mixture of (*E*)-*tert*-butyl 2-(2-hydroxybenzoyl)-3-phenylacrylate **1a** (0.1 mmol) and catalyst **3i** (8 mg, 0.02 mmol) in 1.0 mL of $PhCF_3$ was stirred at room temperature for 24 h until the disappearance of **1a** (monitored by TLC). Then Na_2CO_3 (12.7 mg, 0.12 mmol) and electrophile (0.15 mmol) were added and the mixture was stirred at room temperature for 24–48 h (monitored by TLC). The reaction mixture was then concentrated, and the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether=1/20 to 1/5) to give the desired products **6**, **7**, and **8**.

*4.3.1. tert-Butyl 4-oxo-3-(3-oxobutyl)-2-phenylchroman-3-carboxylate (**6**).* Colorless liquid (39.0 mg, 99% isolated yield, 92% ee). $[\alpha]_D^{24}$ −50.5 (*c* 1.08, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.94–2.10 (m, 2H), 2.13 (s, 3H), 2.42–2.53 (m, 1H), 2.91–3.02 (m, 1H), 5.31 (s, 1H), 7.03 (d, J=8.4 Hz, 1H), 7.08 (t, J=7.8 Hz, 1H), 7.37–7.47 (m, 5H), 7.50 (t, J=7.2 Hz, 1H), 7.95 (d, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 27.7, 29.9, 39.2, 60.2, 83.0, 85.1, 117.5, 121.5, 121.9, 127.6, 128.1, 129.2, 135.0, 135.7, 161.2, 167.1, 191.8, 207.6; MS (EI): *m*/*z* 376 ([M−H_2O]$^+$, 2%), 294 (23), 293 (100), 249 (9), 235 (17), 223 (7), 121 (12), 57 (17), 43 (9); HRMS (EI): *m*/*z* calcd for $C_{24}H_{26}O_5$ (M^+): 394.1780; found: 394.1785; calcd for $C_{24}H_{25}O_4$ ([M−OH]$^+$): 377.1753; found: 377.1752; IR (KBr) ν 2977, 1718, 1688, 1608, 1583, 1464, 1150, 759 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel OD column, hexane/2-propanol: 80/20, flow rate: 0.75 mL/min, t_r (minor)=7.82 min, t_r (major)=9.02 min.

*4.3.2. tert-Butyl 3-bromo-4-oxo-2-phenylchroman-3-carboxylate (**7**).* Colorless liquid (33.0 mg, 82% isolated yield, 93% ee). $[\alpha]_D^{24}$ −142.0 (*c* 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 9H), 5.61 (s, 1H), 7.07 (d, J=8.7 Hz, 1H), 7.15 (t, J=7.5 Hz, 1H), 7.40–7.42 (m, 2H), 7.54–7.59 (m, 3H), 8.05 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 68.9, 85.2, 86.3, 117.7, 119.6, 122.9, 127.6, 127.8, 128.6, 128.7, 129.5, 134.2, 136.5, 160.8, 163.0, 184.3; MS (EI): *m*/*z* 402 (M^+, 7%), 267 (88), 249 (53), 223 (88), 221 (45), 209 (39), 121 (39), 120 (100), 57 (98); HRMS (EI): *m*/*z* calcd for $C_{20}H_{19}O_4Br$ (M^+): 402.0467; found: 402.0470; IR (KBr) ν 2978, 1752, 1698, 1606, 1582, 1463, 1148, 762 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AS-H column, hexane/2-propanol: 80/20, flow rate: 0.75 mL/min, t_r (minor)=7.49 min, t_r (major)=8.09 min.

*4.3.3. tert-Butyl 3-chloro-4-oxo-2-phenylchroman-3-carboxylate (**8**).* Colorless liquid (31.0 mg, 86% isolated yield, 93% ee). $[\alpha]_D^{25}$ −199.8 (*c* 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 9H), 5.49 (s, 1H), 7.10 (d, J=8.4 Hz, 1H), 7.15 (t, J=7.5 Hz, 1H), 7.41–7.42 (m, 2H), 7.55–7.60 (m, 3H), 8.04 (d, J=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 73.7, 85.2, 85.7, 177.8, 119.8, 122.6, 127.9, 128.4, 128.5, 129.5, 133.8, 136.6, 161.0, 162.7, 184.8; MS (EI): *m*/*z* 358 (M^+, 6%), 267 (37), 223 (37), 167 (21), 165 (71), 138 (32), 121 (29), 120 (100), 57 (55); HRMS (EI): *m*/*z* calcd for $C_{20}H_{19}O_4Cl$ (M^+): 358.0792; found: 358.0791; IR (KBr) ν 2978, 1755, 1704, 1606, 1582, 1463, 1149, 762 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel OD column, hexane/2-propanol: 98/2, flow rate: 1.0 mL/min, t_r (minor)=8.39 min, t_r (major)=9.28 min.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.088.

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