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Asymmetric Organocatalytic Quadruple Cascade Reaction of 2-Hydroxychalcone with Cinnamaldehyde for the Construction of Tetrahydro-6*H*-benzo[*c*]chromene Containing Five Stereocenters

Lingyan Liu,*[a] Yunna Zhu,[a] Kaimeng Huang,[a] Bing Wang,[a] Weixing Chang,[a] and Jing Li*[a]

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An asymmetric organocatalytic quadruple cascade reaction was developed for the stable and sterically hindered 2-hydroxychalcones and substituted cinnamaldehydes. This process proceeded through an oxa-Michael–Michael–Michael–aldol condensation to afford highly functionalized tetrahydro-6*H*-benzo[*c*]chromene derivatives with high diastereoselectivity and enantioselectivity (>99 % *ee*). The structure of adduct **4g** with five stereocenters was unambiguously confirmed by single-crystal X-ray diffraction, and valuable mass spectrometry data provided direct support for the proposed reaction mechanism.

Introduction

Chalcone is an α,β-unsaturated carbonyl compound with an aromatic ring at each end, and these aromatic rings, the double bond, and the carbonyl unit can be converted into other functional groups to provide enriched structures and diverse compounds. Hence, chalcone is an important building block in organic synthesis and has a wide potential of applications.[1] Despite this, little research has been done on chalcones because of their low activity and high steric hindrance. Most reports of the last few decades mainly focus on the simple asymmetric Michael reaction of chalcones.[2] To date, higher order asymmetric cascade reactions of the stable chalcone substrate still remain virtually unexplored.

Optically active chiral oxygen- and sulfur-containing compounds, especially chromanes and thiochromanes (see Figure 1), have important applications in many areas of chemistry and biology.[3] Therefore, the exploration of new and facile synthetic strategies to access such heterocycles has attracted intense attention. Vast efforts have been devoted to enantioselective cascade reactions to construct these heterocyclic compounds as a result of the exploration and proliferation of organocatalyzed reactions. However, the scope of the substrates for these reactions is limited to activated cinammaldehydes, α,β-unsaturated esters, nitroalkenes, and *o*-hydroxy- or *o*-thio-substituted aromatic aldehydes (see Figure 2).[4] Moreover, these reactions usually afford a chromane or thiochromane as a binary fused heterocycle with less than three chiral centers, which is formed through an oxa- or sulfa-Michael–Michael or -Michael–aldol cascade reaction. A higher order cascade reaction has hardly been reported in which more than a ternary fused

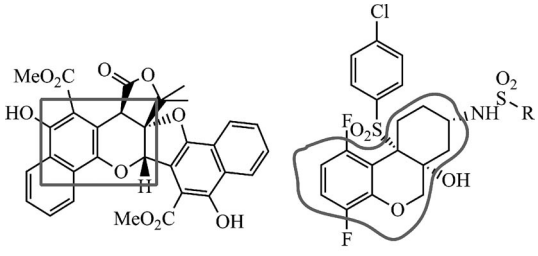

Figure 1. Examples of oxygen-containing natural products.

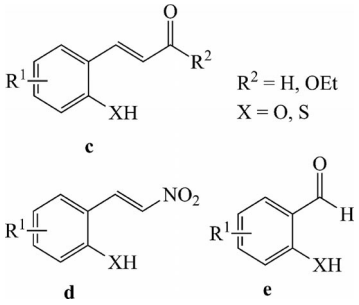

Figure 2. Previously reported substrate types.

[a] State Key Laboratory of Elemento-Organic Chemistry, The College of Chemistry, Nankai University, Collaborative Innovation Center of Chemical Science and Engineering (Tianjin)
Weijin Road 94#, Nankai District, Tianjin 300071, P. R. China
E-mail: lijing@nankai.edu.cn
liulingyan@mail.nankai.edu.cn
http://skleoc.nankai.edu.cn/professors/Lij/index.html

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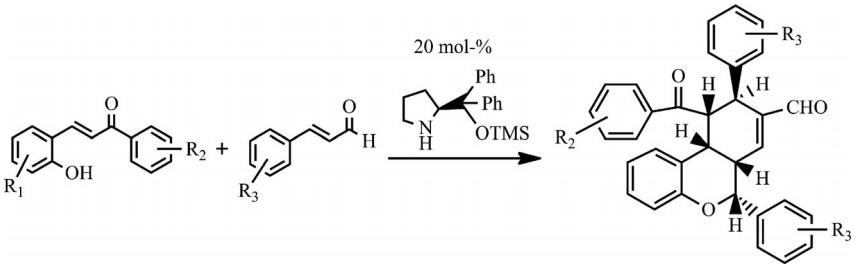


Scheme 1. Organocatalytic enantioselective oxa-Michael–Michael–Michael–aldol cascade reaction.

heterocycle ring is formed with more than three consecutive chiral stereocenters. To the best of our knowledge, there is only one report of a ternary fused cyclic compound that is derived from an activated 2-[(*E*)-2-nitrovinyl]phenol.[5]

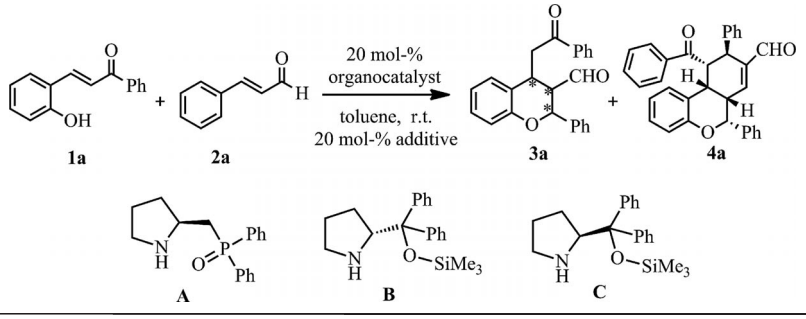
In view of that, it is of considerable interest and a great challenge to develop new and simple synthetic methodology for chalcone derivatives in the construction of multiply fused oxygen-containing heterocycles. As a continuation of our ongoing work to explore new cascade reactions that are catalyzed by organocatalysts,[6] we herein report the enantioselective synthesis of a tetrahydro-6*H*-benzo[*c*]chromene with five contiguous stereocenters. This approach uses chalcone as the starting material and proceeds through a domino oxa-Michael–Michael–Michael–aldol condensation reaction (see Scheme 1).

Results and Discussion

In our initial study, various organocatalysts were examined in the reaction of the simple 2-hydroxychalcone and cinnamaldehyde under the standard reaction conditions (room temperature, toluene, 20 mol-% of organocatalyst, and 20 mol-% of additive). As shown in Table 1, this reaction generally afforded a complex mixture of products **3a** and **4a**. Noteworthy, product such as **3a** is usually obtained in similar asymmetric cascade reactions that have been previously reported, whereas product such as **4a** is difficult to generate.[4] In the presence of (*S*)-2-[(diphenylphosphoryl)-methyl]pyrrolidine (**A**), which displays excellent catalytic activity in the asymmetric Michael addition of a cycloketone and chalcone,[6b] product **3a** was mainly obtained but with a low enantioselectivity (28 %*ee*; see Table 1, Entry 1). When the privileged chiral organocatalyst (*R*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine[7] was used, the enantiomeric excess value of **3a** drastically improved to 93 %*ee*, but the yield was unsatisfactory (see Table 1, Entry 2). Surprisingly, when the absolute configuration of the privileged catalyst was changed from the (*R*) to the (*S*) isomer, no reaction occurred under the same reaction conditions (see Table 1, Entry 3). Nevertheless, when the Lewis base Et_3N was used as an additive, the reaction smoothly proceeded again in the presence of the (*S*)-isomer of the chiral catalyst to result in the good conversion of **3a** and **4a** (33 and 33 %, respectively) with an excellent enantiomeric excess value (97 %*ee*) for product **3a** (see Table 1, Entry 4). An explanation for this phenomenon remains unclear. However, (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine was considered as the optimum chiral catalyst.

Next, the experimental parameters, which included the solvent and additive, were carefully investigated (see

Table 1. The screening of organocatalysts in the reaction of chalcone and cinnamaldehyde.[a]



Entry	Catalyst	Additive	Conv. **3a** [%][b]	Conv. **4a** [%][b]	% *ee* **3a**[c]
1	**A**	PhCOOH	36	14	28
2	**B**	PhCOOH	20	13	93
3	**C**	PhCOOH	trace	trace	–
4	**C**	Et_3N	33	33	97

[a] Into a Schlenk tube were added toluene (0.5 mL), cinnamaldehyde (26.4 mg, 0.2 mmol), and the organocatalyst (0.04 mmol, 0.2 equiv.), and the mixture was stirred at room temperature for 10 min. 2-Hydroxychalcone (67.2 mg, 0.3 mmol) and the additive (0.04 mmol, 0.2 equiv.) were then added. The reaction was monitored by thin layer chromatography. [b] The conversion was calculated by ^{1}H NMR analysis. [c] The enantiomeric excess value was determined by chiral HPLC analysis.

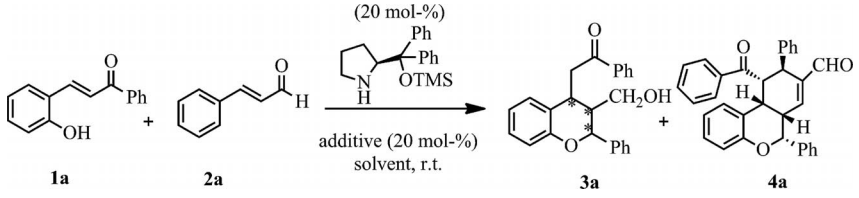
Table 2). As a result, this reaction preferentially afforded product **3a** in 57 % conversion with 97 %*ee* by using $CHCl_3$ instead of toluene (see Table 2, Entry 1 vs. Table 1, Entry 4). When a stronger Lewis base such as 4-(dimethylamino)pyridine (DMAP) was employed, the conversion rate of both **3a** and **4a** slightly increased with a reduced reaction time (see Table 2, entry 2). When the amount of the organocatalyst was decreased, the reaction proceeded poorly with low conversion even after a prolonged reaction time (see Table 2, Entry 3). In the absence of an additive, the reaction yield decreased (see Table 2, Entry 4). Therefore, the optimal reaction conditions involved 20 mol-% of (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine and 20 mol-% of DMAP in $CHCl_3$ (0.4 M).

Because a complex mixture of **3a** and **4a** was always obtained, even with an excess amount of 2-hydroxychalcone, we attempted to adjust the ratio between 2-hydroxychalcone (**1a**) and cinnamaldehyde (**2a**) to achieve a single product. Theoretically, product **4a** is generated from compound **3a** and cinnamaldehyde. Thus, the reaction time was first prolonged from 36 to 72 h. Part of **3a** was indeed further transformed into **4a** (see Table 3, Entries 1 and 2), as there were nearly equal amounts of **3a** and **4a**. Inspired by this, we changed the raw ratio of 2-hydroxychalcone and cinnamaldehyde from 1.5:1 to 1:3. Namely, the cinnamaldehyde substrate was used in an excess amount relative to the 2-hydroxychalcone. As expected, there was more product **4a** than **3a** after 72 h (see Table 3, Entry 3). To our delight, only product **4a** was obtained by using the highly active 2-hydroxy-4′-(trifluoromethyl)chalcone as the substrate (see Table 3, Entry 4).

Encouraged by the above results, we then selected 2-hydroxy-4′-(trifluoromethyl)chalcone as the model substrate. Because of the effect of solvation on the regio- and enantioselectivity, the solvent of this cascade reaction was again examined (see Table 4). The reaction afforded the ternary fused oxygen-containing heterocyclic compounds in moderate yields with excellent enantiomeric excess values (>99 %*ee*) by using weakly polar or nonpolar solvents such as $CHCl_3$, toluene, and CH_2Cl_2 (see Table 4, Entries 1–3). However, the reaction could hardly proceed in the strongly polar solvents of CH_3OH, CH_3CN, and *N*,*N*-dimethylformamide (DMF; see Table 4, Entries 4–6). Therefore, both toluene and $CHCl_3$ were two suitable solvents for this reaction. Toluene was the better solvent in the presence of DMAP as the additive, whereas $CHCl_3$ was preferable when Et_3N was used as the additive. Thus, the combination of $CHCl_3$ with Et_3N was identified to be optimal combination.

The effect of the additive on the reaction was then fine-tuned. As shown in Table 5, when the secondary amine

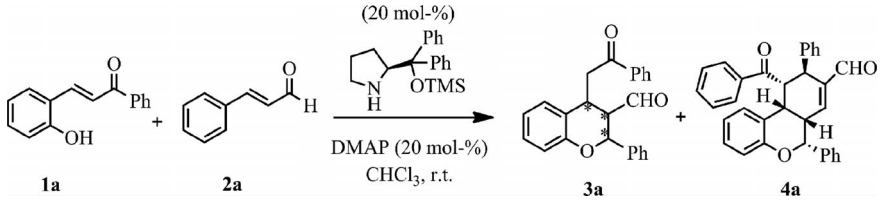
Table 2. The effects of the solvent and additive on the reaction of 2-hydroxychalcone and cinnamaldehyde.



Entry	Solvent	Additive	Time [h]	Conv. **3a** [%][a]	Conv. **4a** [%][a]	% *ee* **3a**[b]
1	$CHCl_3$	Et_3N	48	57	15	97
2	$CHCl_3$	DMAP	36	59	18	96
3[c]	$CHCl_3$	DMAP	72	30	22	97
4	$CHCl_3$	–	36	44	7	97

[a] The conversion rate was calculated by the ^{1}H NMR analysis. [b] The enantiomeric excess value was determined by chiral HPLC analysis. [c] The loading of organocatalyst was 15 mol-%.

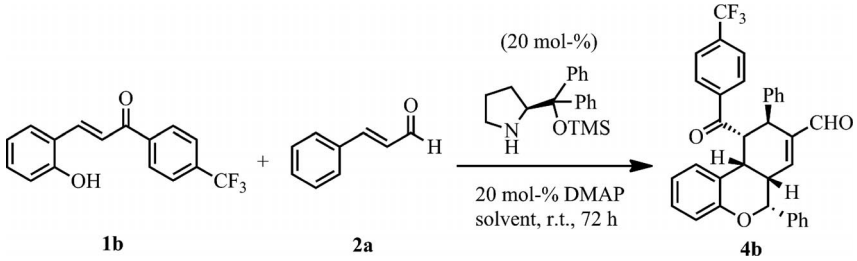
Table 3. Screening for the ratio of substrates in the reaction of 2-hydroxychalcone and cinnamaldehyde.



Entry	**1/2**	Time [h]	**3a/4a**[a]
1	1.5:1	36	**3a** > **4a**
2	1.5:1	72	**3a** = **4a**
3	1:3	72	**3a** < **4a**
4[b]	1:3	72	**4b**

[a] The ratio was determined by ^{1}H NMR analysis. [b] The substrate was 2-hydroxy-4′-(trifluoromethyl)chalcone.

Table 4. The effect of solvent on the asymmetric cascade reaction of 2-hydroxy-4′-(trifluoromethyl)chalcone and cinnamaldehyde.[a]



1b 2a 4b

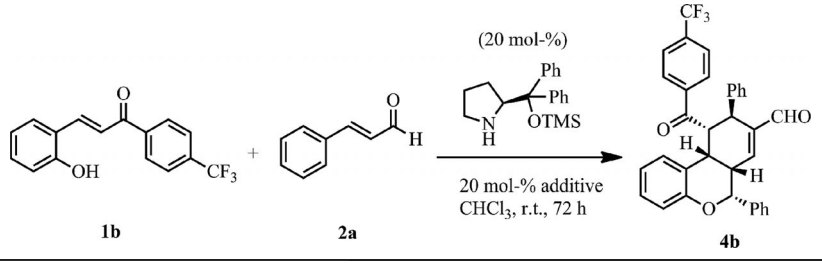
Entry	Solvent	% Yield[b]	% *ee* **4b**[c]
1	$CHCl_3$	47	>99
2	toluene	65	>99
3	CH_2Cl_2	54	>99
4	CH_3OH	trace	–
5	CH_3CN	trace	–
6	DMF	trace	–
7[d]	toluene	61	>99
8[d]	$CHCl_3$	67	>99

[a] Into a Schlenk tube were added solvent (0.5 mL), cinnamaldehyde (79 mg, 0.6 mmol), and (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]-pyrrolidine (0.04 mmol, 0.2 equiv.), and the mixture was stirred at room temperature for 10 min. 2-Hydroxy-4′-(trifluoromethyl)chalcone (58.5 mg, 0.2 mmol) and DMAP (0.04 mmol, 0.2 equiv.) were then added. The reaction was monitored by TLC. Upon completion, the mixture was purified by chromatography on a silica gel column (*n*-hexane/ethyl acetate) to afford the product. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis (Chiralpak AS-H and AD-H columns). [d] The additive was Et_3N.

Et_2NH was employed, the *ee* value remained excellent, but the yield of product decreased slightly (see Table 5, Entry 2). In the presence of iPr_2NEt, no obvious improvement was observed (see Table 5, Entry 3). The reaction proceeded poorly without a Lewis base, although the enantioselectivity of the product was still excellent (see Table 5, Entry 4). On the other hand, when the reaction temperature was increased to 35 °C, the product was obtained in a lower yield (see Table 5, Entry 5). Hence, the optimal reaction conditions employed $CHCl_3$ as the solvent, a chalcone **1** to cinnamaldehyde **2** ratio of 1:3, 20 mol-% of Et_3N, and 20 mol-% of (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine at room temperature.

The scope of the tandem oxa-Michael–Michael–Michael–aldol process was next examined under the optimal reaction conditions with a variety of α,β-unsaturated aldehydes and 2-hydroxychalcone derivatives. As shown in Table 6, all reactions proceeded in 72 h to give products in moderate to good yields (15–74 %) with excellent levels of enantioselectivity (>99 %). The process appeared to have a certain scope of substrates, and the reaction efficiencies varied with the electronic and steric features of the 2-hydroxychalcone derivatives **1** and α,β-unsaturated aldehydes **2**. The 2-hydroxychalcones **1** with different electron-withdrawing groups at the same position, such as 4′-trifluoromethyl, 4′-fluro, and 4′-nitro group (R_2 = 4-CF_3, 4-F, 4-NO_2), gave entirely different reaction results. For example, when R_2 was 4′-CF_3, the reaction proceeded satisfactorily to give ternary fused oxygen-containing heterocyclic compound **4b** in good yield with an excellent *ee* value (see Table 6, Entry 1). With

Table 5. The screening of additives in the asymmetric cascade reaction.

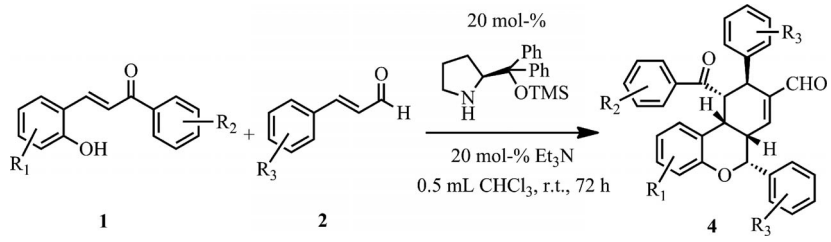


1b 2a 4b

Entry	Additive	% Yield[a]	% *ee* **4b**[b]
1	Et_3N	67	>99
2	Et_2NH	60	>99
3	$(iPr)_2NEt$	66	>99
4	–	18	>99
5[c]	Et_3N	57	>99

[a] Isolated yield. [b] The *ee* value was determined by chiral HPLC analysis. [c] The reaction temperature was 35 °C.

Table 6. The asymmetric cascade reactions of various substituted chalcones and cinnamaldehydes.[a]



Entry	Substrate	Product	% Yield[b]	% *ee* **4**[c]
1	R_1 = H, R_2 = 4-CF_3, R_3 = H	**4b**	67	>99
2[d]	R_1 = H, R_2 = 4-F, R_3 = H	**4c**	15	>99
3	R_1 = H, R_2 = 4-NO_2, R_3 = H	**4d**	n.r.[e]	–
4	R_1 = H, R_2 = 3-CF_3, R_3 = H	**4e**	trace	–
5	R_1 = H, R_2 = 4-CF_3, R_3 = 4-Br	**4f**	54	>99
6	R_1 = H, R_2 = 4-CF_3, R_3 = 4-Cl	**4g**	49	>99
7	R_1 = H, R_2 = 4-CF_3, R_3 = 3-CH_3	**4h**	44	>99
8	R_1 = H, R_2 = 4-CF_3, R_3 = 4-$N(CH_3)_2$	**4i**	n.r	–
9	R_1 = 5-F, R_2 = 4-CF_3, R_3 = H	**4j**	74	>99
10	R_1 = 5-F, R_2 = 4-CF_3, R_3 = 4-Br	**4k**	66	>99
11	R_1 = 5-F, R_2 = 4-CF_3, R_3 = 3-CH_3	**4l**	70	>99
12	R_1 = 3-F, R_2 = 4-CF_3, R_3 = 4-Br	**4m**	n.r.	–
13	R_1 = 3-F, R_2 = 4-CF_3, R_3 = H	**4n**	n.r.	–

[a] Into a Schlenk tube were added $CHCl_3$ (0.5 mL), cinnamaldehyde (0.6 mmol), (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (0.04 mmol, 0.2 equiv.), and the mixture was stirred at room temperature for 10 min. The 2-hydroxychalcone (0.2 mmol) and Et_3N (0.04 mmol, 0.2 equiv.) were then added. The reaction was monitored by TLC. Upon completion, the mixture was purified by chromatography on a silica gel column (*n*-hexane/ethyl acetate) to afford the product. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis. [d] The reaction conversion was determined by ^{1}H NMR spectroscopic analysis. [e] n.r.: no reaction.

the relatively weak electron-withdrawing fluoro group (R_2 = 4′-F), the reaction provided a complex mixture of products **3c** and **4c** (conversion 15 %), although the enantioselectivity remained excellent (see Table 6, Entry 2). For the 4′-nitro-2-hydroxychalcone substrate, with the strong electron-withdrawing group, the reaction could hardly proceed (see Table 6, Entry 3). This demonstrated that fine-tuning the electronic nature of the chalcone substrate would have a large influence on this reaction. Changing the R_2 substitution position from the 4′-CF_3 to 3′-CF_3 led to a trace amount of the target compound (see Table 6, Entry 4). The reactions with chalcone substrate **1b** (R_1 = H, R_2 = 4′-CF_3) and various substituted cinnamaldehydes proceeded smoothly (see Table 6, Entries 5–7). Having electron-withdrawing (R_3 = 4-Br, 4-Cl) and electron-donating (R_3 = 3-CH_3) substituents on the cinnamaldehyde and changing their position of substitution on the aryl ring gave products

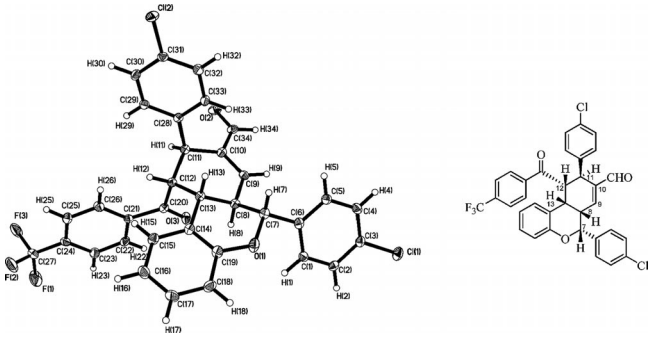


Figure 3. ORTEP plot for X-ray crystal structure of **4g**.

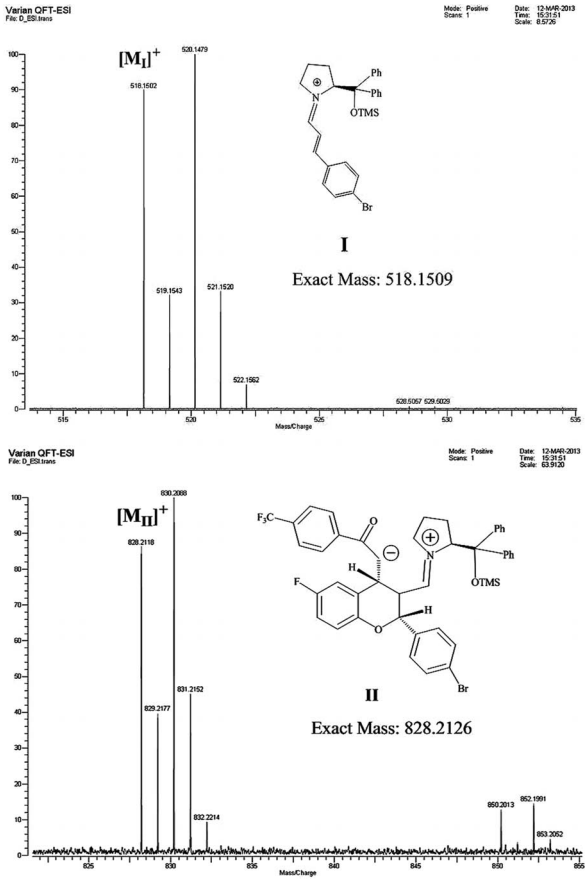
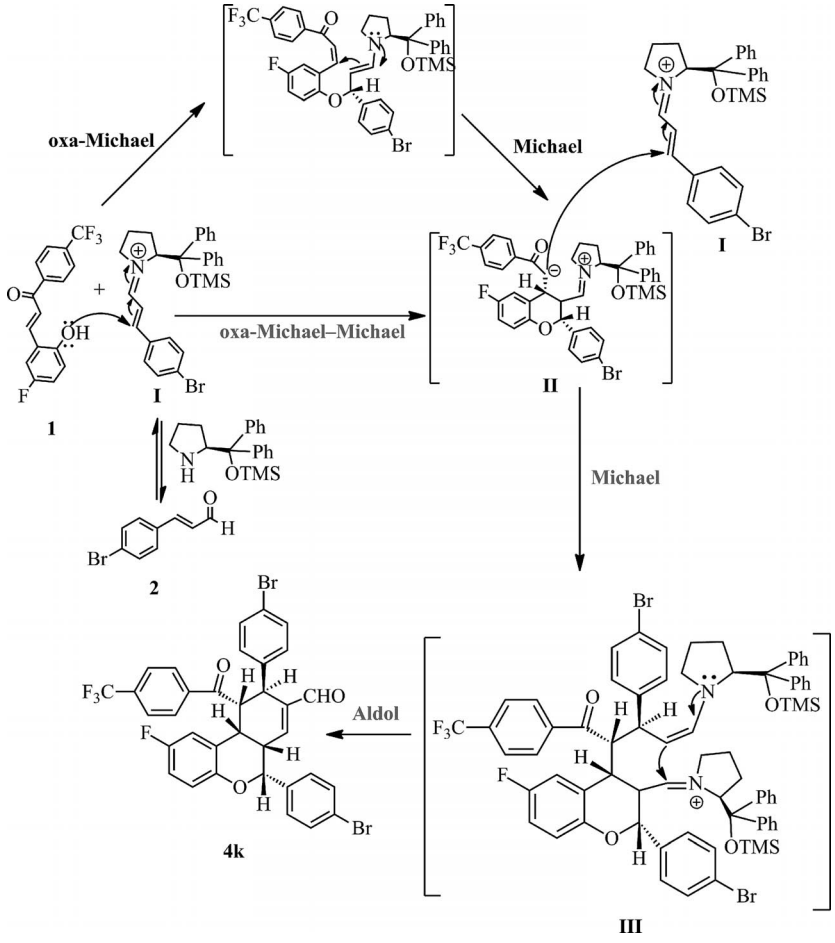


Figure 4. The HRMS spectra of the intermediates **I** (top) and **II** (bottom).

in moderate to good yields with nearly quantitative enantiomeric excess values. However, when R_3 was 4-$N(CH_3)_2$, no reaction occurred (see Table 6, Entry 8). As chalcone has two aryl rings, we attempted to change the other aryl ring, next to the double bond, by introducing a fluoro group at the 5-position. It was encouraging that the reactions between the 5-fluoro-2-hydroxy-4′-(trifluoromethyl)chalcone and various substituted cinnamaldehydes gave improved yields up to 74 % (see Table 6, Entries 9–11). When the fluoro position was changed from 5- to 3-F, that is, 3-fluoro-2-hydroxy-4′-(trifluoromethyl)chalcone, no reaction was observed (see Table 6, Entries 12 and 13). It was further inferred that the position of the substitutent on the aryl ring of chalcone was also a key factor. The above results indicate that both the electronic and steric qualities of the substitutents of 2-hydroxy-α,β-unsaturated ketones **1** dramatically affected the reaction yields, whereas the substituents of α,β-unsaturated aldehydes **2** had a small effect on the reaction.

To determine the absolute configuration of the cascade reaction products, single-crystal structure analysis was carried out by X-ray diffraction. For example, the absolute configurations of the five stereocenters of product **4g** were determined to be (*R*) for C-7, (*S*) for C-8, (*S*) for C-11, (*S*) for C-12, and (*S*) for C-13, and the name of this compound is (6*R*,6a*S*,9*S*,10*S*,10a*S*)-6,9-bis(4-chlorophenyl)-10[4-(trifluoromethyl)benzoyl]-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]-chromene-8-carbaldehyde (see Figure 3).[8]

With regard to the mechanism of this tandem oxa-Michael–Michael–Michael–aldol quadruple reaction, we failed to monitor for intermediates **I** and **II** by NMR spectroscopy. By HRMS analysis, we observed the rapid formation of iminium ion intermediate **I** and the subsequent oxa-Michael–Michael adduct with the activation of iminium ion **II** (see Figure 4). On the basis of this, we proposed the probable reaction mechanism (see Scheme 2). First, the cinnamaldehyde is activated by the chiral catalyst (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine to form iminium ion intermediate **I** [HRMS (found): 518.1509 (518.1502); see Figure 4 (top)]. The hydroxy group of 2-hydroxychalcone **1** then attacks the α-carbon atom on the *re* face of intermediate **I** through an oxa-Michael reaction that is accompanied by a Michael addition between the β-carbon atom of the cinnamaldehyde moiety and the α-carbon atom of the chalcone moiety to give intermediate **II** [HRMS (found): 828.2126 (828.2118); see Figure 4 (bottom)]. The carbon anion of intermediate **II** then undergoes a reaction with a second activated iminium ion **I** through a Michael addition and subsequent intramolecular aldol condensation to obtain intermediate **III**, whereupon the catalyst is re-



Scheme 2. Proposed mechanism for the cascade reaction.

leased for the next cycle along with the formation of compound **4**. For this cascade reaction, it is essential to use a slight excess amount of **2** (e.g., **1/2**, 1:3).

From the above experimental data, we could draw some conclusions. First, the scope of substrates for this quadruple cascade reaction is relatively limited. Second, the Michael reaction in the third step is the key process to construct the ternary fused ring compound. Specifically, the carbon anion of intermediate **II** must be sufficiently nucleophilic to attack the second molecule of intermediate **I**, that is, the cinnamaldehyde that was activated by the organocatalyst. Thus, fine-tuning the substituents on the chalcone by their electronic nature and position would dramatically influence this cascade reaction, and thus explains the limited substrate scope. Finally, the 2-hydroxychalcone with R^2 = 4-CF_3 was the only substrate for which this cascade reaction could occur and afford a sole ternary fused ring product. It is surmised that the electron-withdrawing –CF_3 substituent on the chalcone could indirectly stabilize the carbon anion of intermediate **II** to proceed with the third step of the reaction mechanism.

Conclusions

In summary, we have developed a highly diastereoselective and enantioselective organocatalytic process that proceeds through an oxa-Michael–Michael–Michael–aldol quadruple cascade reaction to construct a ternary fused ring compound. The stable and largely sterically hindered substituted 2-hydroxychalcones were easily prepared and employed as a challenging starting material. Four new bonds and five stereocenters were constructed in the one-pot reaction, which provided expedited access to highly enantiomerically enriched tetrahydro-6*H*-benzo[*c*]chromenes with a substantial diversity of substituents in moderate to good yields with excellent enantiomeric excess values (>99 %*ee*). The structure of adduct **4g** was confirmed by X-ray diffraction analysis. Furthermore, a probable reaction mechanism was proposed on the basis of evidence from HRMS data. Further applications of this approach for the total syntheses of natural products and pharmaceutical agents are currently under active investigation.

Experimental Section

General Methods: The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a Bruker AV 300 or Varian mercury Plus 400. $CDCl_3$ was used as the solvent, and TMS was used as the internal standard, unless otherwise noted. Chemical shifts are reported in ppm, and coupling constants (*J*) are reported in Hz. The enantiomeric excess values were determined by HPLC analysis by using Chiralpak AS-H and AD-H columns (Daicel Chemical Ind., Ltd.) and with *n*-hexane and isopropanol as eluents. All other solvents and commercially available reagents were used as received without further purification, unless otherwise stated. Analytical thin layer chromatography was performed using Merck 60 F_{254} precoated silica gel plates. After elution, the plates were visualized by UV radiation (254 nm) with a Spectroline Model ENF-24061/F (254 nm). The mass spectrometry was performed with a Thermo-Finnigan LCQ-Advantage instrument.

Standard Procedure for the Cascade Reactions of Cinnamaldehydes and 2-Hydroxy-4′-(trifluoromethyl)chalcones: To a Schlenk tube were sequentially added chloroform (0.5 mL), the cinnamaldehyde **2** (0.6 mmol, 3.0 equiv.), and (*S*)-2-[diphenyl(trimethylsilyloxy)-methyl]pyrrolidine (0.04 mmol, 0.2 equiv.), and the mixture was stirred for 10 min. The 2-hydroxy-4′-(trifluoromethyl)chalcones (0.2 mmol, 1.0 equiv.) and the base additive Et_3N (0.04 mmol, 0.2 equiv.) were then added. The reaction was monitored by TLC. Upon completion, the reaction mixture was purified by chromatography on a silica gel column to afford the desired cascade reaction products. The enantiomeric excess value was determined by the HPLC analysis. The procedure for racemic samples was similar to the above reaction conditions, with the exception of using racemic 2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine instead.

Characterization Data of the Cascade Reaction Products

4-(2-Oxo-2-phenylethyl)-2-phenylchroman-3-carbaldehyde (3a): Yellow oil (conversion 57 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.54 (d, *J* = 1.6 Hz, 1 H), 7.69 (d, *J* = 7.8 Hz, 2 H), 7.48–7.43 (m, 2 H), 7.37–7.22 (m, 6 H), 7.13–7.04 (m, 2 H), 6.95–6.84 (m, 2 H), 5.32 (d, *J* = 7.2 Hz, 1 H), 4.12 (dd, *J* = 12.3, 6.9 Hz, 1 H), 4.12 (dd, *J* = 12.3, 6.9 Hz, 1 H), 3.27 (dd, *J* = 6.9, 5.4 Hz, 1 H), 3.13 (dd, *J* = 17.9, 6.3 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.79, 198.42, 154.35, 139.03, 136.59, 133.52, 129.09, 128.69, 128.57, 128.52, 128.22, 128.05, 126.45, 124.05, 121.82, 117.54, 76.42, 56.32, 44.31, 30.29 ppm. MS (ESI): calcd. for $C_{24}H_{20}O_3$ [M – H]$^-$ 355.133; found 355.098. The enantiomeric excess value of >97 % was determined by HPLC analysis. HPLC (Daicel Chiralpak AD; *i*PrOH/hexane, 5:95; wavelength: 254 nm; flow rate: 1.0 mL min^{-1}): t_R = 24.56 min (major), t_R = 28.08 min (minor). (Because of the difficultly isolating **3a** from the complex of **3a** and **4a**, the characterization of **3a** was determined by comparing the corresponding ^{1}H NMR of the racemic product with the ^{1}H NMR of the complex of **3a** and **4a**. The conversion of **3a** was calculated by ^{1}H NMR spectroscopic analysis. For **4a**, we failed to obtain its racemic sample. Thus, the characterization of **4a** cannot be reported at the present time.).

(6*R*,6a*S*,9*S*,10*S*,10a*S*)-6,9-Diphenyl-10-[4-(trifluoromethyl)benzoyl]-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbaldehyde (4b): White solid (72 mg, 67 % yield); m.p. 190–191 °C. $[a]_D^{20}$ = –162 (*c* = 0.77, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (s, 1 H), 8.10 (d, *J* = 8.1 Hz, 2 H), 7.79 (d, *J* = 8.2 Hz, 2 H), 7.55 (d, *J* = 7.2 Hz, 2 H), 7.50–7.41 (m, 3 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.30–7.14 (m, 3 H), 7.01 (t, *J* = 7.6 Hz, 1 H), 6.83 (d, *J* = 8.1 Hz, 1 H), 6.70 (d, *J* = 7.6 Hz, 1 H), 6.64–6.53 (m, 2 H), 5.09 (d, *J* = 10.6 Hz, 1 H), 4.46 (d, *J* = 3.7 Hz, 1 H), 4.13 (s, 1 H), 3.96 (t, *J* = 10.8 Hz, 1 H), 3.54 (dd, *J* = 11.1, 3.5 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.18, 192.47, 155.06, 149.28, 142.11, 140.53, 139.55, 138.66, 135.24, 129.44, 129.22, 128.75, 128.39, 127.86, 127.56, 126.45, 126.42, 123.90, 123.09, 121.95, 120.54, 117.10, 83.63, 46.85, 41.52, 40.42, 34.92 ppm. MS (ESI): calcd. for $C_{34}H_{25}F_3O_3$ [M – H]$^-$ 537.168; found 537.159. The enantiomeric excess value of >99 % was determined by HPLC analysis. HPLC (Daicel Chiralpak AD; *i*PrOH/hexane, 5:95; wavelength: 254 nm; flow rate: 1.0 mL min^{-1}): t_R = 17.44 min (minor), t_R = 21.22 min (major). $C_{34}H_{22}F_3O_3$: calcd. C 75.83, H 4.68; found C 76.07, H 4.56.

(6*R*,6a*S*,9*S*,10*S*,10a*S*)-10-(4-Fluorobenzoyl)-6,9-diphenyl-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbaldehyde (4c): White solid (conversion 15 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (s, 1 H), 8.04 (dd, *J* = 8.7, 5.3 Hz, 2 H), 7.54 (d, *J* = 7.0 Hz, 2 H), 7.50–7.40 (m, 3 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.30–7.15 (m, 7 H),

7.00 (t, J = 8.3 Hz, 1 H), 6.82 (d, J = 8.1 Hz, 1 H), 6.71 (d, J = 7.7 Hz, 1 H), 6.64–6.50 (m, 2 H), 5.09 (d, J = 10.6 Hz, 1 H), 4.41 (d, J = 3.8 Hz, 1 H), 4.13 (s, 1 H), 4.00 (t, J = 10.9 Hz, 1 H), 3.51 (dd, J = 11.1, 3.7 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.51, 192.63, 155.05, 149.43, 142.34, 140.67, 138.75, 131.17, 131.07, 129.38, 129.19, 128.30, 127.88, 127.74, 127.57, 126.44, 123.98, 123.33, 120.49, 117.01, 116.60, 116.38, 83.72, 46.27, 41.59, 40.62, 34.95 ppm. MS (ESI): calcd. for $C_{33}H_{25}FO_3$ [M – H]$^-$ 488.179; found 487.057. The enantiomeric excess value of >99 % was determined by HPLC analysis. HPLC (Daicel Chiralpak AD; *i*PrOH/hexane, 5:95; wavelength: 254 nm; flow rate: 1.0 mL min^{-1}): t_R = 17.24 min (minor), t_R = 47.81 min (major). $C_{33}H_{25}FO_3$: calcd. C 81.13, H 5.16; found C 80.95, H 5.35. (In this case, we obtained a complex of **3c** and **4c**, and they were difficult to separate by column chromatography. Thus, the conversion was determined by ^{1}H NMR analysis.)

(6*R*,6a*S*,9*S*,10*S*,10a*S*)-6,9-Bis(4-bromophenyl)-10-[4-(trifluoromethyl)benzoyl]-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbaldehyde (4f): White solid (75 mg, 54 % yield); m.p. 203–204 °C. $[\alpha]_D^{20}$ = –112 (c = 1.46, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (s, 1 H), 8.13 (d, J = 7.6 Hz, 2 H), 7.86 (d, J = 7.7 Hz, 2 H), 7.69 (d, J = 7.7 Hz, 2 H), 7.52 (dd, J = 17.3, 7.8 Hz, 4 H), 7.22–7.02 (m, 3 H), 6.89 (d, J = 7.9 Hz, 1 H), 6.77 (d, J = 7.1 Hz, 1 H), 6.70–6.64 (m, 2 H), 5.11 (d, J = 10.4 Hz, 1 H), 4.48 (s, 1 H), 4.13 (s, 1 H), 4.00 (t, J = 10.6 Hz, 1 H), 3.53 (d, J = 9.8 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.86, 192.19, 154.72, 148.94, 141.08, 140.42, 139.34, 137.51, 135.33, 135.01, 132.54, 132.40, 129.52, 129.17, 128.65, 128.54, 126.50, 126.46, 124.91, 123.92, 123.46, 122.53, 122.20, 121.84, 120.80, 117.10, 82.68, 46.48, 41.23, 39.87, 34.81 ppm. MS (ESI): calcd. for $C_{34}H_{23}Br_2F_3O_3$ [M – H]$^-$ 694.987; found 695.129. The enantiomeric excess value of >99 % was determined by HPLC analysis. HPLC (Daicel Chiralpak AD; *i*PrOH/hexane, 5:95; wavelength: 254 nm; flow rate: 1.0 mL min^{-1}): t_R = 26.51 min (minor), t_R = 39.87 min (major). $C_{34}H_{23}Br_2F_3O_3$: calcd. C 58.64, H 3.33; found C 58.60, H 3.50.

(6*R*,6a*S*,9*S*,10*S*,10a*S*)-6,9-Bis(4-chlorophenyl)-10-[4-(trifluoromethyl)benzoyl]-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbaldehyde (4g): White solid (60 mg, 49 % yield); m.p. 171–172 °C. $[\alpha]_D^{20}$ = –138 (c = 1.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (s, 1 H), 8.14 (d, J = 8.1 Hz, 2 H), 7.86 (d, J = 8.2 Hz, 2 H), 7.55 (q, J = 8.6 Hz, 4 H), 7.39 (d, J = 8.3 Hz, 2 H), 7.21 (d, J = 8.3 Hz, 2 H), 7.09 (t, J = 7.6 Hz, 1 H), 6.89 (d, J = 8.1 Hz, 1 H), 6.78 (d, J = 7.6 Hz, 1 H), 6.69 (t, J = 7.4 Hz, 1 H), 6.64 (s, 1 H), 5.12 (d, J = 10.6 Hz, 1 H), 4.49 (d, J = 3.6 Hz, 1 H), 4.16 (s, 1 H), 4.00 (t, J = 10.8 Hz, 1 H), 3.54 (dd, J = 11.1, 3.4 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.90, 192.17, 154.77, 148.90, 140.57, 140.51, 139.41, 137.03, 135.33, 135.30, 135.01, 133.79, 129.59, 129.45, 129.22, 128.83, 128.65, 128.53, 126.49, 124.93, 123.94, 122.59, 122.22, 120.79, 117.11, 82.66, 46.62, 41.31, 39.82, 34.86 ppm. MS (ESI): calcd. for $C_{34}H_{23}Cl_2F_3O_3$ [M – H]$^-$ 605.090; found 605.074. The enantiomeric excess value of >99 % was determined by HPLC analysis. HPLC (Daicel Chiralpak AD; *i*PrOH/hexane, 5:95; wavelength: 254 nm; flow rate: 1.0 mL min^{-1}): t_R = 25.77 min (minor), t_R = 33.25 min (major). $C_{34}H_{23}Cl_2F_3O_3$: calcd. C 67.23, H 4.35; found C 66.62, H 3.82.

(6*R*,6a*S*,9*S*,10*S*,10a*S*)-6,9-Di-*m*-tolyl-10-[4-(trifluoromethyl)-benzoyl]-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbaldehyde (4h): White solid (50 mg, 44 % yield); m.p. 179–180 °C. $[\alpha]_D^{20}$ = –155 (c = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1 H), 8.19 (d, J = 8.1 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H), 7.49–7.37 (m, 3 H), 7.31 (t, J = 7.7 Hz, 2 H), 7.19–7.04 (m, 4 H), 6.89 (t, J = 12.6 Hz, 1 H), 6.79 (d, J = 7.6 Hz, 1 H), 6.72–6.62 (m, 2 H), 5.13 (d, J = 10.6 Hz, 1 H), 4.53 (d, J = 3.6 Hz, 1 H), 4.18 (s, 1 H), 4.05 (t, J = 10.8 Hz, 1 H), 3.62 (dd, J = 11.1, 3.5 Hz, 1 H), 2.49 (s, 3 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.32, 192.59, 155.06, 149.34, 142.07, 140.50, 139.58, 139.10, 138.51, 135.18, 134.86, 130.25, 129.22, 129.02, 128.75, 128.64, 128.35, 128.33, 128.27, 126.40, 125.12, 124.62, 123.94, 123.11, 122.29, 120.46, 117.07, 83.68, 46.86, 41.30, 40.34, 34.94, 21.84, 21.70 ppm. MS (ESI): calcd. for $C_{36}H_{29}F_3O_3$ [M – H]$^-$ 565.158; found 565.141. The enantiomeric excess value of >99 % was determined by HPLC analysis. HPLC (Daicel Chiralpak AD; *i*PrOH/hexane, 3:97; wavelength: 254 nm; flow rate: 1.0 mL min^{-1}): t_R = 10.02 min (minor), t_R = 15.86 min (major). $C_{36}H_{29}F_3O_3$: calcd. C 76.31, H 5.16; found C 76.45, H 5.31.

(6*R*,6a*S*,9*S*,10*S*,10a*S*)-2-Fluoro-6,9-diphenyl-10-[4-(trifluoromethyl)benzoyl]-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbaldehyde (4j): White solid (83 mg, 74 % yield); m.p. 217–218 °C. $[\alpha]_D^{20}$ = –157 (c = 2.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (s, 1 H), 8.19 (d, J = 8.1 Hz, 2 H), 7.88 (d, J = 8.2 Hz, 2 H), 7.63 (d, J = 7.1 Hz, 2 H), 7.59–7.50 (m, 3 H), 7.44 (t, J = 7.4 Hz, 2 H), 7.39–7.27 (m, 3 H), 6.85 (dd, J = 8.9, 4.9 Hz, 1 H), 6.77 (td, J = 8.6, 2.5 Hz, 1 H), 6.65 (s, 1 H), 6.54–6.46 (m, 1 H), 5.15 (d, J = 10.5 Hz, 1 H), 4.45 (d, J = 3.2 Hz, 1 H), 4.25 (s, 1 H), 4.07 (t, J = 10.8 Hz, 1 H), 3.59 (dd, J = 11.1, 3.0 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.93, 192.30, 158.02, 155.64, 150.98, 148.80, 141.89, 140.44, 139.32, 138.36, 135.28, 134.95, 129.44, 129.20, 128.69, 127.89, 127.78, 127.48, 126.48, 124.94, 124.37, 124.30, 122.23, 117.98, 117.89, 114.89, 114.66, 110.77, 110.53, 83.44, 47.13, 41.17, 40.39, 34.87 ppm. MS (ESI): calcd. for $C_{34}H_{24}F_4O_3$ [M – H]$^-$ 555.158; found 555.197. The enantiomeric excess value of >99 % was determined by HPLC analysis. HPLC (Daicel Chiralpak AD; *i*PrOH/hexane, 3:97; wavelength: 254 nm; flow rate: 1.0 mL min^{-1}): t_R = 26.08 min (minor), t_R = 29.57 min (major). $C_{34}H_{24}F_4O_3$: calcd. C 73.37, H 4.35; found C 73.13, H 4.22.

(6*R*,6a*S*,9*S*,10*S*,10a*S*)-6,9-Bis(4-bromophenyl)-2-fluoro-10-[4-(trifluoromethyl)benzoyl]-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbaldehyde (4k): White solid (94 mg, 66 % yield); m.p. 177–178 °C. $[\alpha]_D^{20}$ = –130 (c = 0.83, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (s, 1 H), 8.12 (d, J = 8.1 Hz, 2 H), 7.87 (d, J = 8.1 Hz, 2 H), 7.69 (d, J = 8.2 Hz, 2 H), 7.51 (dd, J = 21.0, 8.2 Hz, 4 H), 7.13 (d, J = 8.2 Hz, 2 H), 6.89–6.72 (m, 2 H), 6.61 (s, 1 H), 6.48 (d, J = 7.0 Hz, 1 H), 5.08 (d, J = 10.5 Hz, 1 H), 4.37 (d, J = 3.4 Hz, 1 H), 4.15 (s, 1 H), 4.00 (t, J = 10.8 Hz, 1 H), 3.49 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.62, 192.02, 158.15, 155.77, 150.73, 148.48, 140.88, 140.41, 139.18, 137.25, 135.48, 135.15, 132.60, 132.44, 129.48, 129.11, 128.63, 126.57, 124.87, 123.85, 123.78, 123.56, 121.94, 118.12, 118.04, 115.17, 114.94, 110.82, 110.59, 82.60, 46.83, 40.96, 39.91, 34.84 ppm. MS (ESI): calcd. for $C_{34}H_{22}Br_2F_4O_3$ [M – H]$^-$ 712.977; found 713.401. The enantiomeric excess value of >99 % was determined by HPLC analysis. HPLC (Daicel Chiralpak AD; *i*PrOH/hexane, 5:95; wavelength: 254 nm; flow rate: 1.0 mL min^{-1}): t_R = 27.80 min (minor), t_R = 33.52 min (major). $C_{34}H_{22}Br_2F_4O_3$: calcd. C 57.17, H 3.10; found C 56.96, H 2.98.

(6*R*,6a*S*,9*S*,10*S*,10a*S*)-2-Fluoro-6,9-di-*m*-tolyl-10-[4-(trifluoromethyl)benzoyl]-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbaldehyde (4l): White solid (982 mg, 70 % yield); m.p. 212–213 °C. $[\alpha]_D^{20}$ = –130 (c = 1.43, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1 H), 8.08 (d, J = 8.1 Hz, 2 H), 7.77 (d, J = 8.2 Hz, 2 H), 7.41–7.25 (m, 3 H), 7.26–7.12 (m, 2 H), 7.05 (d, J = 7.5 Hz, 1 H), 7.01–6.91 (m, 2 H), 6.80–6.60 (m, 2 H), 6.53 (s, 1 H),

6.39 (dd, J = 8.9, 2.3 Hz, 1 H), 4.99 (d, J = 10.5 Hz, 1 H), 4.32 (d, J = 3.6 Hz, 1 H), 4.09 (s, 1 H), 3.95 (t, J = 10.8 Hz, 1 H), 3.48 (dd, J = 11.1, 3.2 Hz, 1 H), 2.39 (s, 3 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.09, 192.41, 158.03, 155.65, 151.04, 148.87, 141.88, 140.47, 139.39, 139.16, 138.26, 135.31, 134.98, 130.33, 129.26, 129.05, 128.73, 128.29, 128.24, 126.43, 125.07, 124.53, 122.25, 117.99, 117.91, 114.87, 114.64, 110.81, 110.57, 83.56, 77.48, 41.02, 40.36, 34.95, 21.82, 21.68 ppm. MS (ESI): calcd. for $C_{36}H_{28}F_4O_3$ $[M - H]^-$ 583.190; found 583.208. The enantiomeric excess value of >99 % was determined by HPLC analysis. HPLC (Daicel Chiralpak AD; *i*PrOH/hexane, 3:97; wavelength: 254 nm; flow rate: 1.0 mL min^{-1}): t_R = 9.71 min (minor), t_R = 13.31 min (major). $C_{34}H_{24}F_4O_3$: calcd. C 73.96, H 4.83; found C 73.34, H 5.39.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data of chalcones as well as ^{1}H and ^{13}C NMR spectra, HPLC, XRD, and crystal data of the corresponding ternary fused cyclic products.

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[8] Crystal data for product **4g**: $C_{34}H_{23}Cl_2F_3O_3$, formula mass: 607.42 g mol^{-1}, rhombohedral, a = 27.5799(11) Å, b = 27.5799(11) Å, c = 10.2741(8) Å, α = 90°, β = 90°, γ = 120°, unit cell volume = 6768.0(7) Å^3, T = 113(2) K, space group = $R3$, Z = 9, no. of reflections measured = 22373, no. of independent reflections = 7068, R_{int} = 0.0484, final R_1 values [$I > 2\sigma(I)$] = 0.0580, final $wR(F^2)$ values [$I > 2\sigma(I)$] = 0.1525, final R_1 values (all data) = 0.0676, final $wR(F^2)$ values (all data) = 0.1586. CCDC-976415 (for **4g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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