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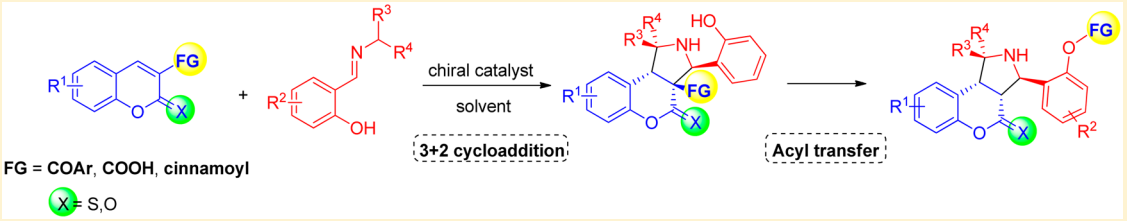
Enantioselective Synthesis of Polysubstituted Benzopyrano[3,4-*c*]pyrrolidine Frameworks via [3 + 2] Cycloaddition of Azomethine Ylides and Coumarin Derivatives

Geng-Hua Chang,[†] Chein-Yi Wang,[†] G. Madhusudhan Reddy, Yi-Ling Tsai, and Wenwei Lin*

Department of Chemistry, National Taiwan Normal University, Taipei 11677, Taiwan, R.O.C.

Supporting Information



ABSTRACT: An enantioselective synthesis of benzopyrano[3,4-*c*]pyrrolidine derivatives via organocatalyzed [3 + 2] cycloaddition has been achieved. Cinchona alkaloid-derived organocatalysts as Brønsted bases have been examined for this asymmetric cycloaddition of *o*-hydroxy aromatic aldimines with 3-substituted coumarins. An unexpected rearrangement of the quaternary acyl moiety in the products resulted in an *in situ* protection of the *o*-hydroxy group.

Since almost a century, [3 + 2] cycloaddition has served as one of the most indispensable and powerful methods for the construction of multiple C−C and C−X bonds. This strategy allows the concise synthesis of a variety of fused five-membered heterocycles.[1] Among the 1,3-dipolar systems used for such cycloadditions, azomethine ylides have emerged as one of the most common ones, resulting in fused pyrrolidines.[2] There have been a variety of olefins that have been utilized as dipolarophiles in conjunction with azomethine ylides. However, coumarins, both activated and unactivated, have been seldom used as dipolarophiles in such [3 + 2] cycloadditions,[3] owing to their low reactivity and reluctance to lose their aromatic-like nature. However, if exploited well, the potential of these systems can be used to develop new fused-ring tricyclic frameworks which could have therapeutic and pharmaceutical importance (Figure 1).[4]

In 2010, Xie et al. used a thiourea-derived bifunctional organocatalyst for the kinetic resolution of 3-nitro-chromenes to obtain chiral chromeno[4,3-*b*]pyrrolidines.[5] Later, in 2014, Hui et al. synthesized the pyrrolo[3,2-*c*]quinolines via a Michael−Mannich-lactamization cascade of *o*-aminoaromatic aldimines and 2-bromoenals.[6] In addition, Xie[7] and Waldmann[8] independently reported the synthesis of benzopyrano[3,4-*c*]pyrrolidines via the [3 + 2] cycloaddition of coumarins and *α*-iminoesters (Scheme 1). However, their strategy could not impart any enantioselectivity in the products and the substrate tolerance was quite limited. It prompted us to attempt for the development of an enantioselective format of the reaction to obtain chiral benzopyrano[3,4-*c*]pyrrolidines.

In order to construct two C−C bonds and three vicinal stereogenic centers at the same time, 3-benzoyl coumarin derivative **1aa** and *o*-hydroxy aromatic aldimine **2a** were initially

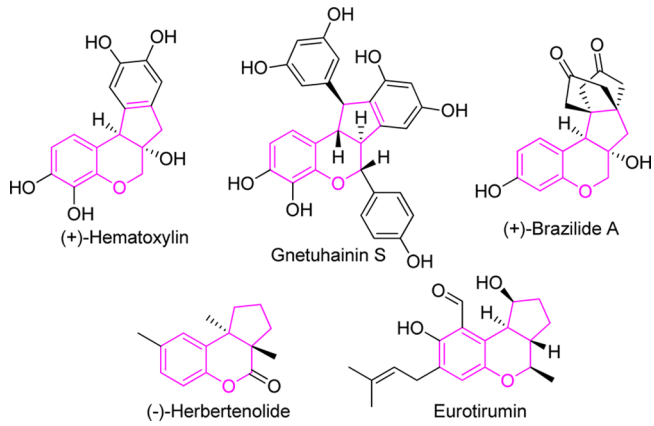


Figure 1. Tricyclic natural products containing a benzopyran ring.

treated with DABCO in toluene at room temperature (Table 1, entry 1). Our initial objective while employing the substrate bearing an *o*-hydroxy substitution in aldimine was to study the possibility of further cyclization.[9] To our delight, the reaction proceeded well and a single diastereomer was formed in 99% yield. However, the spectroscopic data of the product revealed that the product obtained was neither of the two expected ones. It was rather the cycloaddition product **3aaa** that was formed by a further migration of the acyl group at the quaternary stereocenter of the pyranone ring onto the *o*-hydroxy substitution. This rearrangement could prove to be quite useful as it resulted in the products with an *in situ* protection of the

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Scheme 1. Michael Addition/Mannich Reaction Cascade

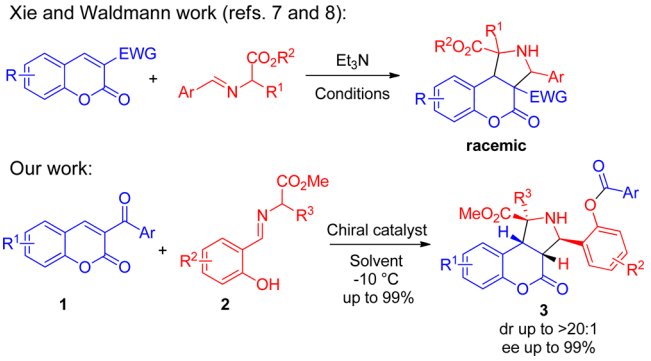
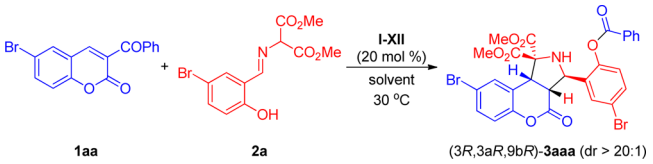


Table 1. Screening of Catalysts and Solvents[a]



entry	cat.	solvent	time	yield (%)[b]	ee (%)[c]
1	DABCO	toluene	50 min	99	
2	**I**	toluene	50 min	99	49[d]
3	**II**	toluene	90 min	99	55
4	**III**	toluene	23 h	93	12
5	**IV**	toluene	50 min	89	10[d]
6	**V**	toluene	24 h	70	3[d]
7	**VI**	toluene	3 h	94	8
8	**VII**	toluene	15 h	54	2
9	**VIII**	toluene	2.5 h	92	48
10	**IX**	toluene	50 min	95	37[d]
11	**X**	toluene	50 min	86	29
12	**XI**	toluene	50 min	95	27[d]
13[e]	**XII**	toluene	70 min	97	22
14	**II**	THF	30 min	96	50
15	**II**	DCM	40 min	95	40
16	**II**	EA	35 min	99	60
17	**II**	EtOH	30 min	96	5
18	**II**	MeCN	35 min	97	56
19	**II**	DMSO	60 min	75	44
20	**II**	DMF	40 min	90	63
21	**II**	NMP	50 min	84	71

[a]Reactions were performed using **1aa** (0.1 mmol), **2a** (1.0 equiv), and cat. (20 mol %) in the corresponding solvent (0.5 mL). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard. [c]Determined by HPLC analysis on a chiral stationary phase. [d]*ent*-**3aaa** was obtained. [e]In the presence of 20 mol % of K_2CO_3.

phenolic group. Thus, formed phenolic esters could have useful applications for further transformations such as acyl-directed CH activation[11] and Fries rearrangement.[12]

Encouraged by this result, the enantioselective reactions were examined using different cinchona alkaloid-derived chiral catalysts **I**–**IX** (Table 1, entries 2–10; Figure 2), along with the thiourea catalysts **X** and **XI** (Table 1, entries 11 and 12) and the phase transfer catalyst **XII** (Table, entry 13). The best result was obtained with **II** (Table 1, entry 3), which furnished **3aaa** in 99% yield and 55% enantiomeric excess.

An extensive screening of the reaction was further carried out by varying different parameters such as solvent, temperature,

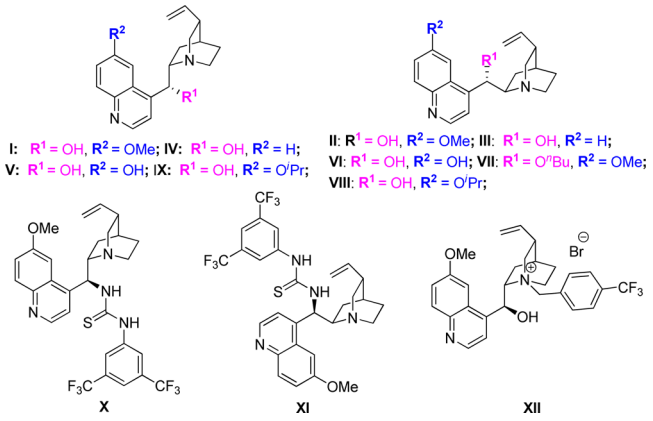
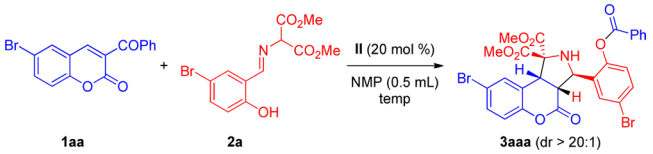


Figure 2. Catalysts screened during optimization.

catalyst loadings, and concentration. As solvent, NMP was found to give the best result with enhanced enantioinduction (Table 1, entry 21). Then, the effect of varying temperatures, which happens to be a key factor in cycloaddition reactions, was tested. Lowering the reaction temperature resulted in better enantioselectivity (Table 2). The optimal conditions for this

Table 2. Screening of Additional Reaction Parameters[a]



entry	temp (°C)	time	yield (%)[b]	ee (%)[c]
1	30	50 min	84	71
2	0	4.5 h	82	82
3[d]	0	3.5 h	94	84
4[d]	−10	8 h	94	90
5[d,e]	−10	5 h	96	87
6[d]	−20	18 h	98	89
7[d,e]	−20	13 h	96	87
8[d,f]	−10	24 h	92	88

[a]Reactions were performed on **1aa** (0.1 mmol), **2a** (1.0 equiv), and **II** (20 mol %) in NMP (0.5 mL). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard. [c]Determined by HPLC analysis on a chiral stationary phase. [d]1.1 equiv of **2a** was used. [e]0.2 mL of NMP was used. [f]10 mol % of **II** was used.

enantioselective cascade reaction were found (Table 2, entry 4), where we could obtain **3aaa** with high yield and excellent diastereoselectivity and enantiomeric induction. When the reaction was carried out at lower temperature, formation of the intermediate could be observed by TLC analysis. However, it could not be isolated and characterized because of its high reactivity and converted into the product **3aaa** as soon as the reaction mixture was quenched with HCl.

We then tried to evaluate the substrate scope of this [3 + 2] cycloaddition by varying the substituents on coumarins **1** and aldimines **2**, and the results are presented in Table 3. In most cases, the reaction proceeded well with excellent diastereocontrol. The presence of a methyl ester functionality resulted in slightly better enantioselectivity when compared to the ethyl ester (Table 3, entries 1 and 2). Replacing the R^1 substituent on coumarin **1** with either the electron-withdrawing or the electron-donating groups led to varied reactivities and

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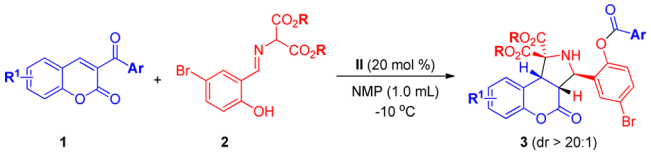
Table 3. Substrate Scope for the Enantioselective Cascade Reactions[a]



1 2 3 (dr > 20:1)

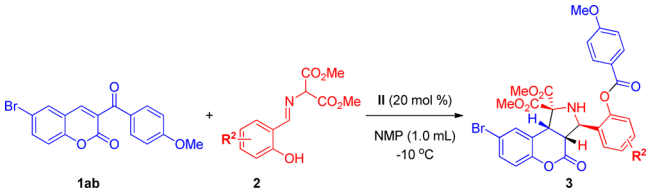
entry	R^1/Ar	R	time	3, yield (%)[b]	ee (%)[c]
1	6-Br/Ph	Et	9.5 h	**3aaa′** (96)	83
2	6-Br/Ph	Me	8 h	**3aaa** (94)	90
3	6-NO_2/Ph	Me	2.5 h	**3baa** (97)	76
4	6,8-Cl_2/Ph	Me	3.5 h	**3caa** (94)	91
5	H/Ph	Me	3 d	**3daa** (77)	88
6	8-OMe/Ph	Me	3 d	**3eaa** (62)	80
7	7-OMe/Ph	Me	5 d	**3faa** (60)	85
8	6-OMe/Ph	Me	2.5 d	**3gaa** (95)	85
9	6-NO_2/4-OMePh	Me	1 d	**3bba** (63)	79
10	6-Br/4-OMePh	Me	5 h	**3aba** (82)	>99[d]
11	6-Br/4-NO_2Ph	Me	50 h	**3aca** (65)	84
12	6-Br/3-NO_2Ph	Me	78 h	**3ada** (77)	74
13	6-Br/4-BrPh	Me	16 h	**3aea** (95)	86
14	6-Br/2-naphthyl	Me	15 d	**3afa** (13)[e]	ND
15	6-Br/2-thienyl	Me	29 h	**3aga** (91)	87
16	6-Br/styryl	Me	4 d	**3aha** (60)	80

[a]Reactions were performed using **1** (0.2 mmol), **2** (1.1 equiv), and **II** (20 mol %) in NMP (1.0 mL) at −10 °C. [b]Isolated yields. [c]Determined by HPLC analysis on a chiral stationary phase. [d]CCDC No. 1401439. [e]NMR yield as determined by ^{1}H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard. ND = not determined.

selectivities, indicating that both the steric and the electronic factors played a vital role in the final outcome of this reaction (Table 3, entries 3−8). Likewise, modifying the substitution on the Ar group of coumarin also displayed subtle differences in the reaction outcome as it would influence both the course of [3 + 2] cycloaddition as well as the migration of the acyl group (Table 3, entries 9−16). The substrate with a 2-naphthyl substitution displayed poor reactivity and yielded only a trace amount of the product (Table 3, entry 14). Interestingly, the heteroaryl functionality such as the thienyl group could be tolerated well and resulted in the cycloddition product in good yield and enantioselectivity (Table 3, entry 15). An α,β-unsaturated system such as a cinnamoyl group could also favor the reaction, resulting in the product **3aha** in moderate yield and good enantioselectivity (Table 3, entry 16). However, when the aryl group was replaced by either a methyl or a cyclohexyl group, the reaction did not proceed and the expected product could not be obtained. The absolute configuration of **3aba** was established as (3*R*,3a*R*,9b*R*) by X-ray crystallographic analysis,[10] and that of other products was assigned by analogy.

We then carried out the reaction by varying the substitution on the aryl ring of α-iminoester **2**, and the results are shown in Table 4. The nature and position of the substitution displayed a great influence on the outcome of the reaction. A substitution at the 3rd or 4th position on the aromatic ring greatly reduced the reactivity and also resulted in the products with poor enantioselectivities (Table 4, entries 4−6). In the case of a substitution at the 3rd position, formation of two diastereomers could be observed. From these results, it could be derived that the presence of a functional group that has the ability to disrupt

Table 4. Scope of the Enantioselective Cascade Reaction with Different Imines[a]



1ab 2 3

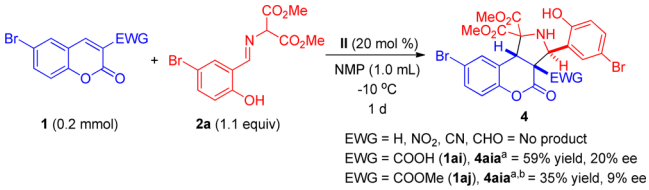
entry	R^2	time	3, yield (%)[b]	dr[c]	ee (%)[d]
1	5-Br	5 h	**3aba** (82)	>20:1	>99
2	H	12 h	**3abb** (75)	>20:1	72
3	5-OMe	12 h	**3abc** (88)	>20:1	12
4	4-OMe	10 d	**3abd** (68)	>20:1	59
5	3-OMe	10 d	**3abe** (52)	2:1	30
6	3,5-Cl_2	10 d	**3abf** (30)	3:2	14

[a]Reactions were performed using **1ab** (0.2 mmol), **2** (1.1 equiv), and **II** (20 mol %) in NMP (1.0 mL) at −10 °C. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis on a chiral stationary phase.

the hydrogen bonding interactions between the carbonyl function of the EWG and the catalyst would destabilize the transition state and result in poor reactivity as well as stereoselectivity.

We then tried to test the significance of different EWGs in **1** in the course of the [3 + 2] cyclization. Although no reaction was expected in the absence of an EWG, it was surprising to see that the expected products could not be obtained even in the presence EWGs such as NO_2, CN, or CHO, and the starting materials could be recovered even after extended reaction times (Scheme 2). However, the presence of a carboxylic acid group

Scheme 2. Study of 1 with Different EWGs for the Enantioselective Cascade Reaction



[a]Decarboxylated product was obtained. [b]Reaction at 30 °C.

could promote the [3 + 2] cyclization well, but resulted in the decarboxylated product **4aia** in 59% yield and poor enantioselectivity. Likewise, even the presence of an ester as EWG resulted in the same decarboxylated product **4aia** in poor yield and enantioselectivity.

The reaction worked well even with the comparatively less nucleophilic imine **5** bearing a single ester functionality that displayed good reactivity, resulting in product **6aa** with a quaternary stereocenter as a 9:1 mixture of diastereomers in good yield with moderate enantioselectivity (Scheme 3).

The thiocoumarin derivative **7aa** could also be employed well in our designed reaction, furnishing the product **8aaa** as a single diastereomer in 79% yield and 91% ee, thereby demonstrating the broad substrate applicability of this reaction (Scheme 4). The reaction could also be carried out on a 5 mmol scale with similar efficiency, affording the product **3aaa** in good yield and enantioselectivity (Scheme 5). The plausible mechanism for the subsequent rearrangement of the acyl group of the initially

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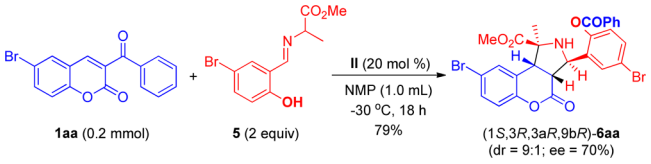
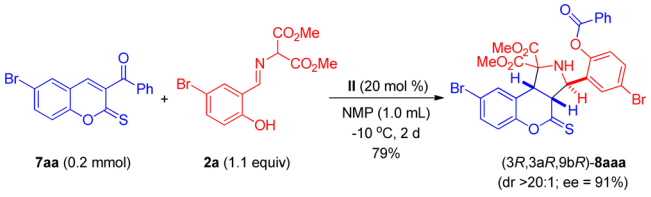
Scheme 3. Reaction with Less Nucleophilic Imine 5

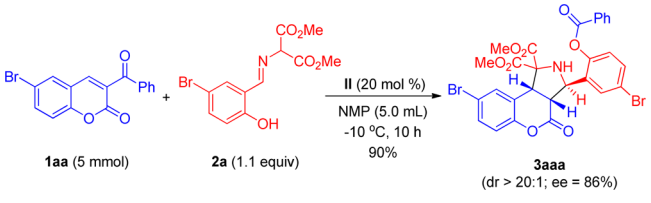


Scheme 4. Reaction with Thiocoumarin Derivative 7aa

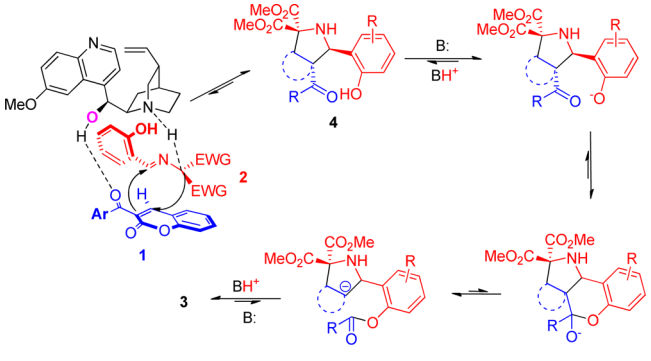


formed [3 + 2] cycloaddition adduct **4** is presented in Scheme 6.

Scheme 5. Scaling-Up of the Reaction



Scheme 6. Plausible Mechanism for the Enantioselective Cascade Reaction



In summary, we have successfully demonstrated an organocatalytic enantioselective [3 + 2] cycloaddition for the construction of chiral chromenopyrrolidines from α-iminoester and coumarin derivatives. It is the first time that the coumarin derivatives have been used in conjunction with azomethine ylides for the enantioselective synthesis of corresponding fused pyrrolidines. Furthermore, the products formed were susceptible toward an *in situ* rearrangement of the acyl group, resulting in the protection of the phenolic functionality, which could help in further functionalization of the aryl ring.

EXPERIMENTAL SECTION

General Experimental Methods. All solvents and reagents were used as purchased from commercial suppliers without further purification. Starting materials and catalysts which were not commercially available were synthesized by the previously reported methods. Analytical thin-layer chromatography (TLC) was performed on precoated alumina-backed silica gel plates (0.2 mm thickness) which were developed using UV florescence and iodine. Flash chromatography was performed on silica gel (230−400 mesh). Melting points were measured on a standard melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer, while ^{13}C NMR spectra were recorded on a 100 MHz instrument. Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^{1}H NMR and chloroform-*d* (δ = 77.0 ppm) for ^{13}C NMR. HRMS spectra were recorded using FAB (TOF analyzer) or ESI (TOF analyzer). The X-ray diffraction measurements were carried out at 298 K on a CCD area detector system equipped with a graphite monochromator and a Mo−Kα fine-focus sealed tube (*k* = 0.71073 Å). Optical rotations were measured in $CHCl_3$ on a polarimeter with a 50 mm cell (*c* given in g/100 mL) operating at λ = 589 nm, corresponding to the sodium D line, at the indicated temperatures.

Characterization Data for New Compounds. *TP-1: Typical Procedure for the Synthesis of New Substrates **1ae**−**1ag** from 5-Bromosalicylaldehyde and Different Substituted Ethyl Benzoylacetates.* Piperidine (5 mol %) was added to a stirred solution of 5-bromosalicylaldehyde (10 mmol) and the corresponding ethyl benzoylacetate (1.25 equiv) in CH_3CN (10 mL) at room temperature. After stirring for 5 min, the contents were heated to 80 °C for 8 h. After the reaction was completed, the reaction mixture was allowed to cool to room temperature, solvent was removed *in vacuo*, and the crude product was purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent to get the pure product **1ae**−**1ag**.

*6-Bromo-3-(4-bromobenzoyl)-2H-chromen-2-one (**1ae**).*[13] Following the typical procedure **TP-1**, the desired product **1ae** was obtained as a white solid (2962.9 mg, 73%). mp 142.4−143.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ/ppm 8.40 (s, 1H), 8.11 (s, 1H), 7.94−7.83 (m, 3H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ/ppm 190.5, 157.5, 153.2, 144.4, 135.8, 134.9, 131.7, 131.6, 131.4, 128.1, 126.8, 120.1, 118.5, 116.2. IR (ATR, cm^{-1}): ν̃ = 1750, 1732, 1606, 1234, 932, 767. HRMS (ESI) for $C_{16}H_9Br_2O_3$ $[M + H]^+$ calc.: 406.8918; found: 406.8917.

*3-(2-Naphthoyl)-6-bromo-2H-chromen-2-one (**1af**).*[14] Following the typical procedure **TP-1**, the desired product **1af** was obtained as a white solid (2305.7 mg, 61%). mp 205.8−206.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.33 (s, 1H), 8.01 (s, 1H), 7.99−7.85 (m, 4H), 7.79−7.69 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 9.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 191.0, 157.8, 153.6, 143.6, 136.2, 136.1, 133.3, 132.3, 132.1, 131.3, 129.7, 129.1, 128.7, 128.4, 127.9, 127.0, 124.5, 119.7, 118.7, 117.6. IR (ATR, cm^{-1}): ν̃ = 1627, 1362, 1195, 657. HRMS (ESI) for $C_{20}H_{12}BrO_3$ $[M + H]^+$ calc.: 378.9970; found: 378.9972.

*6-Bromo-3-(thiophene-2-carbonyl)-2H-chromen-2-one (**1ag**).* Following the typical procedure **TP-1**, the desired product **1ag** was obtained as a pale yellow solid (1636.2 mg, 49%). mp 205.1−206.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.00 (s, 1H), 7.78 (d, *J* = 4.1 Hz, 1H), 7.77−7.68 (m, 3H), 7.31 (d, *J* = 9.7 Hz, 1H), 7.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 182.4, 157.5, 153.4, 143.1, 142.6, 136.3, 136.0, 135.3, 131.2, 128.4, 127.9, 119.5, 118.7, 117.6. IR (ATR) ν̃ (cm^{-1}) 2116, 1623, 1272, 696. HRMS (ESI) for $C_{14}H_8BrO_3SNa$ $[M + Na]^+$ calc.: 356.9197; found: 356.9194.

*TP-2: Typical Procedure for the Preparation of Starting Materials **2a′** and **2a**−**2f**.* To a solution of dialkyl aminomalonate hydrochloride (3.0 mmol) in H_2O (6 mL) was added $NaHCO_3$ (3.3 mmol), and the mixture was stirred for 15 min. Then, the reaction mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to afford the corresponding dialkyl aminomalonate. This was used directly in the next step without further purification.

The crude dialkyl aminomalonate was dissolved in DCM (5.0 mL), and $MgSO_4$ (5.0 equiv) and the respective substituted benzaldehyde (2.0 mmol) were added and stirred for 48 h. Then, $MgSO_4$ was removed by filtration and the solvent was removed *in vacuo* to get the crude product which was recrystallized from DCM/hexanes to afford the pure product **2**.

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*(E)-Diethyl 2-((5-Bromo-2-hydroxybenzylidene)amino)malonate (**2a′**).*[15] Following the typical procedure **TP-2**, the desired product **2a′** was obtained as yellow crystals (451.0 mg, 63%). mp 106.8−107.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.42 (s, 1H), 7.43 (t, J = 7.8 Hz, 2H), 6.89 (d, J = 9.6 Hz, 1H), 4.88 (s, 1H), 4.30 (q, J = 7.2 Hz, 4H), 1.32 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 168.5, 165.9, 160.0, 136.0, 134.2, 119.8, 119.3, 110.2, 72.4, 62.5, 13.9. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3414, 2985, 1739, 1633, 1476, 1402, 1369, 1276, 1178, 1097, 1027, 821, 750. HRMS (ESI) for $C_{14}H_{15}BrNO_5$ [M − H]$^-$ calc.: 356.0134; found: 356.0132.

*(E)-Dimethyl 2-((5-Bromo-2-hydroxybenzylidene)amino)-malonate (**2a**).* Following the typical procedure **TP-2**, the desired product **2a** was obtained as yellow crystals (449.0 mg, 68%). mp 85.6−86.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.41 (s, 1H), 7.51−7.39 (m, 2H), 6.91 (d, J = 9.5 Hz, 1H), 4.92 (s, 1H), 3.85 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 168.8, 166.2, 160.0, 136.1, 134.3, 119.8, 119.4, 110.3, 72.2, 53.4, 53.3. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3454, 2359, 1737, 1637, 1478, 1334, 1272, 1244, 1166, 1115, 982, 825. HRMS (FAB) for $C_{12}H_{13}BrNO_5$ [M + H]$^+$ calc.: 329.9977; found: 329.9982.

*(E)-Dimethyl 2-((2-Hydroxybenzylidene)amino)malonate (**2b**).* Following the typical procedure **TP-2**, the desired product **2b** was obtained as yellow crystals (417.8 mg, 83%). mp 62.0−62.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 12.60 (s, 1H), 8.47 (s, 1H), 7.37 (dt, J = 7.8, 1.3 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.92 (t, J = 7.8 Hz, 1H), 4.90 (s, 1H), 3.84 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 170.0, 166.6, 161.1, 133.6, 132.4, 118.9, 118.5, 117.4, 72.7, 53.3. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3456, 2961, 1731, 1624, 1456, 1404, 1315, 1268, 1174, 1090, 1022, 763. HRMS (FAB) for $C_{12}H_{14}NO_5$ [M + H]$^+$ calc.: 252.0872; found: 252.0871.

*(E)-Dimethyl 2-((2-Hydroxy-5-methoxybenzylidene)amino)-malonate (**2c**).* Following the typical procedure **TP-2**, the desired product **2c** was obtained as reddish yellow crystals (389.8 mg, 69%). mp 65.0−65.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 12.15 (s, 1H), 8.44 (s, 1H), 6.99 (dd, J = 9.0, 2.8 Hz, 1H), 6.94 (d, 1H, J = 9.0 Hz), 6.82 (d, 1H, J = 2.8 Hz), 4.90 (s, 1H), 3.84 (s, 6H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 169.8, 166.5, 155.3, 152.2, 121.0, 118.2, 115.3, 115.2, 72.7, 55.9, 53.3. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3446, 2958, 1738, 1634, 1589, 1380, 1278, 1215, 1161, 1094, 1030, 795. HRMS (FAB) for $C_{13}H_{16}NO_6$ [M + H]$^+$ calc.: 282.0978; found: 282.0968.

*(E)-Dimethyl 2-((2-Hydroxy-4-methoxybenzylidene)amino)-malonate (**2d**).* Following the typical procedure **TP-2**, the desired product **2d** was obtained as yellow crystals (269.9 mg, 48%). mp 66.8−67.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.35 (s, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.48−6.42 (m, 2H), 4.84 (s, 1H), 3.83−3.79 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 168.8, 166.7, 164.0, 163.4, 133.5, 112.3, 106.8, 101.0, 72.2, 55.3, 53.0. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3451, 3006, 1742, 1613, 1508, 1392, 1286, 1227, 1172, 1112, 1022, 830. HRMS (FAB) for $C_{13}H_{16}NO_6$ [M + H]$^+$ calc.: 282.0976; found: 282.0966.

*(E)-Dimethyl 2-((2-Hydroxy-3-methoxybenzylidene)amino)-malonate (**2e**).* Following the typical procedure **TP-2**, the desired product **2e** was obtained as yellow crystals (320.4 mg, 57%). mp 63.8−64.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.44 (s, 1H), 6.97−6.88 (m, 2H), 6.80 (t, J = 7.8 Hz, 1H), 4.80 (s, 1H), 3.86 (s, 3H), 3.78 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 169.9, 166.4, 151.1, 148.3, 123.7, 118.4, 118.3, 115.1, 72.3, 56.1, 53.2, 53.1. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3706, 3006, 1742, 1613, 1508, 1395, 1286, 1228, 1172, 1112, 1022, 830. HRMS (FAB) for $C_{13}H_{16}NO_6$ [M + H]$^+$ calc.: 282.0978; found: 282.0974.

*(E)-Dimethyl 2-((3,5-Dichloro-2-hydroxybenzylidene)amino)-malonate (**2f**).* Following the typical procedure **TP-2**, the desired product **2f** was obtained as orange colored crystals (456.3 mg, 72%). mp 92.2−92.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 13.44 (s, 1H), 8.43 (s, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.25 (d, J = 2.4 Hz, 1H), 4.95 (s, 1H), 3.85 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 168.4, 165.9, 155.7, 133.2, 129.9, 123.4, 122.9, 119.6, 71.8, 53.5. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3459, 2957, 1747, 1636, 1451, 1380, 1340, 1243, 1180, 1166, 1121, 844. HRMS (FAB) for $C_{12}H_{12}Cl_2NO_5$ [M + H]$^+$ calc.: 320.0093; found: 320.0098.

*TP-3: Typical Procedure for the Preparation of Compound **3**.* In a glass vial equipped with a magnetic stirring bar were added **1** (0.20 mmol), quinidine (20 mol %), and NMP (1 mL), and the mixture was cooled to −10 °C. Then, **2** (0.22 mmol) was added and stirred at the same temperature, and the progress of the reaction was monitored by TLC and ^{1}H NMR analysis. After the completion of the reaction, the reaction mixture was neutralized with 1 N HCl and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel to afford the desired product **3**.

*TP-4: Typical Procedure for the Preparation of rac-**3**.* In a glass vial equipped with a magnetic stir bar were added **1** (0.20 mmol), **2** (1.1 equiv), DABCO (20 mol %), and toluene (1.0 mL), and the mixture was stirred at 30 °C. The reaction was monitored by TLC and ^{1}H NMR analysis. After the completion of the reaction, the reaction mixture was neutralized with 1 N HCl and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel to afford the desired product *rac*-**3**.

*(3R,3aR,9bR)-Diethyl 3-(2-(Benzoyloxy)-5-bromophenyl)-8-bromo-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3aaa′**).* Prepared according to the typical procedure **TP-3** using 3-benzoyl-6-bromo-2*H*-chromen-2-one[16] **1aa** (65.8 mg, 0.2 mmol), (*E*)-diethyl 2-((5-bromo-2-hydroxybenzylidene)amino)-malonate **2a′** (78.5 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3aaa′** as a white solid (132.0 mg, 96%). mp 179.1−180.3 °C. 83% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 8.46 min, t_{major} = 17.48 min). $[\alpha]_D^{25}$ = +5.352 (c = 0.5, CH_2Cl_2). R_f: 0.35 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.19 (d, J = 7.6 Hz, 2H), 7.76 (t, J = 2.3 Hz, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.54−7.44 (m, 3H), 7.36 (dd, J = 8.6, 2.2 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 5.72 (d, J = 6.9 Hz, 1H), 4.47−4.32 (m, 3H), 3.91−3.68 (m, 2H), 3.39 (d, J = 8.0 Hz, 1H), 3.21 (d, J = 8.0 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.2, 169.2, 165.6, 165.2, 150.1, 147.0, 137.9, 133.8, 133.4, 132.4, 131.6, 130.9, 130.4, 128.7, 128.5, 124.5, 119.8, 118.3, 116.9, 76.5, 62.9, 62.5, 57.9, 48.6, 42.5, 14.0, 13.2. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3447, 1735, 1640, 1479, 1350, 1262, 1168, 707. HRMS (ESI) for $C_{30}H_{26}Br_2NO_8$ [M + H]$^+$ calc.: 685.9912; found: 685.9914.

*(3R,3aR,9bR)-Dimethyl 3-(2-(Benzoyloxy)-5-bromophenyl)-8-bromo-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3aaa**).* Prepared according to the typical procedure **TP-3** using 3-benzoyl-6-bromo-2*H*-chromen-2-one[16] **1aa** (65.8 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)-malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3aaa** as a white solid (123.9 mg, 94%). mp 163.8−165.0 °C. 90% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 10.01 min, t_{major} = 15.62 min). $[\alpha]_D^{25}$ = +4.231 (c = 0.5, CH_2Cl_2). R_f: 0.28 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.19 (dd, J = 7.2, 1.3 Hz, 2H), 7.74 (dd, J = 7.2, 2.4 Hz, 2H), 7.68−7.61 (m, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.47 (dd, J = 6.2, 2.4 Hz, 1H), 7.37 (dd, J = 6.2, 2.4 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 5.72 (s, 1H), 4.36 (d, J = 8.9 Hz, 1H), 3.92 (s, 3H), 3.34 (s, 3H), 3.21 (dd, J = 7.4, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.6, 169.5, 165.6, 165.4, 150.1, 147.0, 137.9, 133.9, 133.3, 132.7, 131.8, 130.9, 130.4, 128.7, 128.6, 124.7, 119.8, 119.7, 118.3, 117.1, 57.9, 53.5, 53.1, 48.5, 42.7. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3451, 2925, 1733, 1638, 1476, 706. HRMS (ESI) for $C_{28}H_{22}Br_2NO_8$ [M + H]$^+$ calc.: 657.9715; found: 657.9714.

*(3R,3aR,9bR)-Dimethyl 3-(2-(Benzoyloxy)-5-bromophenyl)-8-nitro-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3baa**).* Prepared according to the typical procedure **TP-3** using 3-benzoyl-6-nitro-2*H*-chromen-2-one[17] **1ba** (59.0 mg, 0.2

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mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)-malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3baa** as a pale yellow solid (121.3 mg, 97%). mp 228.8−230.1 °C. 76% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 22.53 min, t_{major} = 33.89 min). $[\alpha]_D^{25}$ = −1.691 (*c* = 0.5, CH_2Cl_2). R_f: 0.15 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.53 (d, *J* = 2.4 Hz, 1H), 8.23−8.13 (m, 3H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.57−7.46 (m, 3H), 7.08 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 5.71 (d, *J* = 6.8 Hz, 1H), 4.46 (d, *J* = 8.8 Hz, 1H), 3.94 (s, 3H), 3.36 (s, 3H), 3.32 (d, *J* = 6.8 Hz, 1H), 3.29 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.3, 169.1, 165.4, 164.7, 155.3, 147.0, 144.1, 137.5, 134.0, 132.0, 130.9, 130.4, 128.6, 128.6, 126.7, 125.3, 124.7, 119.8, 118.8, 117.5, 76.5, 57.8, 53.6, 53.1, 48.0, 42.7. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3365, 2954, 1736, 1594, 1529, 1438, 1169, 749. HRMS (ESI) for $C_{28}H_{22}BrN_2O_{10}$ $[M + H]^+$ calc.: 625.0458; found: 625.0453.

*(3R,3aR,9bR)-Dimethyl 3-(2-(Benzoyloxy)-5-bromophenyl)-6,8-dichloro-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1-(9bH)-dicarboxylate (**3caa**).* Prepared according to the typical procedure **TP-3** using 3-benzoyl-6,8-dichloro-2*H*-chromen-2-one[17] **1ca** (63.8 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3caa** as a white solid (121.3 mg, 94%). mp 185.1−186.5 °C. 91% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 97/3, flow rate = 1.0 mL/min, t_{minor} = 26.46 min, t_{major} = 29.36 min). $[\alpha]_D^{25}$ = −1.611 (*c* = 0.5, CH_2Cl_2). R_f: 0.38 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.20 (d, *J* = 2.4 Hz, 2H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.69−7.63 (m, 1H), 7.56−7.46 (m, 4H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 5.73 (s, 1H), 4.39 (d, *J* = 8.8 Hz, 1H), 3.92 (s, 3H), 3.40 (s, 3H), 3.32 (dd, *J* = 7.0, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.2, 169.4, 165.4, 164.5, 147.0, 145.8, 137.7, 134.0, 131.9, 130.9, 130.4, 130.1, 129.5, 128.8, 128.6, 124.7, 122.3, 120.6, 119.8, 57.9, 53.5, 53.2, 48.4, 43.0. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3424, 1779, 1734, 1632, 1458, 1143, 758, 709. HRMS (M + H) for $C_{28}H_{21}BrCl_2NO_8$ $[M + H]^+$ calc.: 647.9828; found: 647.9818.

*(3R,3aR,9bR)-Dimethyl 3-(2-(Benzoyloxy)-5-bromophenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3daa**).* Prepared according to the typical procedure **TP-3** using 3-benzoyl-2*H*-chromen-2-one[17] **1da** (50.0 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2- hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3daa** as a pale yellow solid (89.4 mg, 77%). mp 156.8−157.1 °C. 88% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 9.48 min, t_{major} = 14.49 min). $[\alpha]_D^{25}$ = −2.912 (*c* = 0.5, CH_2Cl_2). R_f: 0.31 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.24−8.19 (m, 2H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.59 (dd, *J* = 6.3, 2.4 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.47 (dd, *J* = 6.3, 2.4 Hz, 1H), 7.29−7.23 (m, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 5.75 (d, *J* = 6.3 Hz, 1H), 4.42 (d, *J* = 8.9 Hz, 1H), 3.91 (s, 3H), 3.36 (d, *J* = 6.9 Hz, 1H), 3.28 (s, 3H), 3.25 (dd, *J* = 7.5 1.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.8, 169.9, 166.2, 165.3, 150.9, 147.0, 138.1, 133.9, 131.6, 131.0, 130.6, 130.4, 129.6, 128.8, 128.6, 124.6, 119.7, 117.4, 116.6, 58.1, 53.3, 52.9, 49.0, 43.0. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3367, 2927, 1737, 1473, 1352, 1261, 1169, 760, 711. HRMS (ESI) for $C_{28}H_{23}BrNO_8$ $[M + H]^+$ calc.: 580.0607; found: 580.0615.

*(3R,3aR,9bR)-Dimethyl 3-(2-(Benzoyloxy)-5-bromophenyl)-6-methoxy-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3eaa**).* Prepared according to the typical procedure **TP-3** using 3-benzoyl-8-methoxy-2*H*-chromen-2-one[18] **1ea** (56.0 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)-malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3eaa** as a white solid (75.5 mg, 62%). mp 220.9−222.0 °C. 80% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 17.78 min, t_{major} = 31.46 min). $[\alpha]_D^{25}$ = −1.87 (*c* = 0.5, CH_2Cl_2). R_f: 0.13 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.20 (d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 2.2 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.54−7.44 (m, 3H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.08−7.02 (m, 2H), 6.85 (d, *J* = 7.9 Hz, 1H), 5.77 (d, *J* = 6.7 Hz, 1H), 4.42 (d, *J* = 8.8 Hz, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.39 (d, *J* = 7.5 Hz, 1H), 3.33 (s, 3H), 3.22 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.6, 170.0, 165.5, 165.3, 147.2, 147.0, 140.4, 138.1, 133.9, 131.6, 131.0, 130.5, 128.7, 128.6, 124.6, 124.4, 121.9, 119.6, 118.4, 112.0, 58.2, 56.0, 53.4, 52.9, 48.8, 43.2. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3408, 2378, 1638, 1390, 1260. HRMS (ESI) $C_{29}H_{25}BrNO_9$ $[M + H]^+$ calc.: 610.0613; found: 610.0610.

*(3R,3aR,9bR)-Dimethyl 3-(2-(Benzoyloxy)-5-bromophenyl)-7-methoxy-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3faa**).* Prepared according to the typical procedure **TP-3** using 3-benzoyl-7-methoxy-2*H*-chromen-2-one[18] **1fa** (56.0 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)-malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3faa** as a white solid (73.1 mg, 60%). mp 204.1−205.8 °C. 85% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 13.42 min, t_{major} = 19.43 min). $[\alpha]_D^{25}$ = +4.048 (*c* = 0.5, CH_2Cl_2). R_f: 0.12 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.21 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 2.6 Hz, 1H), 7.68−7.61 (m, 1H), 7.55−7.45 (m, 4H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.67 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.47 (d, *J* = 2.6 Hz, 1H), 5.72 (s, 1H), 4.36 (d, *J* = 8.8 Hz, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.33 (s, 3H), 3.22 (dd, *J* = 8.8, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.9, 170.0, 166.2, 165.4, 160.5, 151.7, 147.0, 138.2, 133.8, 131.6, 131.3, 131.0, 130.4, 128.8, 128.6, 124.6, 119.7, 110.9, 109.0, 101.8, 57.9, 55.5, 53.3, 52.9, 49.1, 42.7. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3437, 1732, 1626, 1469, 1268. HRMS (ESI) $C_{29}H_{25}BrNO_9$ $[M + H]^+$ calc.: 610.0613; found: 610.0610.

*(3R,3aR,9bR)-Dimethyl 3-(2-(Benzoyloxy)-5-bromophenyl)-8-methoxy-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3gaa**).* Prepared according to the typical procedure **TP-3** using 3-benzoyl-6-methoxy-2*H*-chromen-2-one[18] **1ga** (56.1 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)-malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3gaa** as a white solid (116.0 mg, 95%). mp 175.6−176.1 °C. 85% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 11.66 min, t_{major} = 16.26 min). $[\alpha]_D^{25}$ = −2.592 (*c* = 0.5, CH_2Cl_2). R_f: 0.13 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.21 (d, *J* = 7.7 Hz, 2H), 7.76 (d, *J* = 2.2 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.47 (dd, *J* = 6.2, 2.5 Hz, 1H), 7.11 (d, *J* = 2.8 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.79 (dd, *J* = 6.3, 2.8 Hz, 1H), 5.73 (d, *J* = 6.3 Hz, 1H), 4.36 (d, *J* = 8.7 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.35 (d, *J* = 7.0 Hz, 1H), 3.32 (s, 3H), 3.20 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.7, 169.8, 166.3, 165.3, 156.1, 147.0, 144.8, 138.2, 133.8, 131.6, 130.9, 130.4, 128.8, 128.5, 124.6, 119.6, 118.1, 117.3, 115.7, 114.5, 58.0, 55.7, 53.3, 52.9, 48.8, 43.2. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3456, 2955, 1735, 1643, 1495, 1264, 1056, 707. HRMS (ESI) for $C_{29}H_{25}BrNO_9$ $[M + H]^+$ calc.: 610.0713; found: 610.0710.

*(3R,3aR,9bR)-Dimethyl 3-(5-Bromo-2-((4-methoxybenzoyl)oxy)-phenyl)-8-nitro-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3bba**).* Prepared according to the typical procedure **TP-3** using 3-(4-methoxybenzoyl)-6-nitro-2*H*-chromen-2-one[19] **1bb** (65.1 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3bba** as a white solid (82.6 mg, 63%). mp 174.9−176.1 °C.

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79% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 36.25 min, t_{major} = 47.99 min). $[\alpha]_D^{25}$ = +7.488 (*c* = 0.5, CH_2Cl_2). R_f: 0.13 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.53 (d, *J* = 2.6 Hz, 1H), 8.17 (dd, *J* = 9.1, 2.6 Hz, 1H), 8.15 (d, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 2.6 Hz, 1H), 7.48 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.06 (dd, *J* = 18.2, 8.9 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 5.71 (d, *J* = 6.7 Hz, 1H), 4.45 (d, *J* = 9.1 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.36 (s, 3H), 3.32 (d, *J* = 6.9 Hz, 1H), 3.28 (dd, *J* = 8.9, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.3, 169.2, 165.1, 164.8, 164.2, 155.4, 147.1, 144.1, 137.5, 132.6, 132.0, 130.8, 126.7, 125.3, 124.8, 120.8, 119.6, 118.9, 117.5, 113.9, 57.9, 55.5, 53.7, 53.2, 48.1, 42.8. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3428, 2926, 1730, 1636, 1529, 1464, 1257, 1164, 739. HRMS (ESI) for $C_{29}H_{24}BrN_2O_{11}$ $[M + H]^+$ calc.: 655.0563; found: 655.0532.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(5-bromo-2-((4-methoxybenzoyl)oxy)phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3aba**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-(4-methoxybenzoyl)-2*H*-chromen-2-one[17] **1ab** (71.6 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3aba** as a yellow solid (112.7 mg, 82%). mp 210.9−212.1 °C. >99% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 16.62 min, t_{major} = 20.45 min). $[\alpha]_D^{25}$ = +41.968 (*c* = 0.5, CH_2Cl_2). R_f: 0.25 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.15 (d, *J* = 9.2 Hz, 2H), 7.75 (d, *J* = 2.5 Hz, 2H), 7.48 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.38 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.4, 1H), 5.74 (s, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.37 (s, 3H), 3.22 (dd, *J* = 8.8, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.5, 169.6, 165.6, 165.0, 164.2, 150.1, 147.1, 137.8, 133.3, 132.6, 131.7, 130.8, 124.8, 120.9, 119.7, 118.2, 117.1, 113.9, 58.0, 55.5, 53.4, 53.0, 48.6, 42.8. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3425, 1735, 1634, 1477, 1401, 1263, 1070,751. HRMS (ESI) for $C_{29}H_{24}Br_2NO_9$ $[M + H]^+$ calc.: 687.9818; found: 687.9812.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(5-bromo-2-((4-nitrobenzoyl)oxy)phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3aca**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-(4-nitrobenzoyl)-2*H*-chromen-2-one[17] **1ac** (74.6 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3aca** as a white solid (91.3 mg, 65%). mp 227.1−228.3 °C. 84% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 28.22 min, t_{major} = 33.22 min). $[\alpha]_D^{25}$ = +27.432 (*c* = 0.5, CH_2Cl_2). R_f: 0.25 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.56 (q, *J* = 6.3, 4H), 7.78 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.49 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.38 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 5.69 (d, *J* = 6.5 Hz, 1H), 4.37 (d, *J* = 9.0 Hz, 1H), 3.93 (s, 3H), 3.34 (s, 3H), 3.29 (d, *J* = 9.0 Hz, 1H), 3.16 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.6, 169.2, 165.8, 163.6, 150.8, 149.8, 146.4, 138.0, 134.2, 133.2, 132.7, 131.9, 131.4, 130.9, 124.2, 123.6, 120.3, 119.3, 118.1, 117.2, 76.5, 57.4, 53.4, 53.0, 48.4, 42.4. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3370, 2953, 1740, 1606, 1528, 1476, 1409, 1070. HRMS (ESI) for $C_{28}H_{21}Br_2N_2O_{10}$ $[M + H]^+$ calc.: 702.9577; found: 702.9576.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(5-bromo-2-((3-nitrobenzoyl)oxy)phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3ada**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-(3-nitrobenzoyl)-2*H*-chromen-2-one **1ad**[17] (74.8 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3ada** as a white solid (108.5 mg, 77%). mp 239.2−240.1 °C. 74% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 25.10 min, t_{major} = 32.32 min). $[\alpha]_D^{25}$ = +19.981 (*c* = 0.5, CH_2Cl_2). R_f: 0.24 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 9.01 (t, *J* = 1.9 Hz, 1H), 8.56−8.46 (m, 2H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.78−7.71 (m, 2H), 7.50 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.38 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 5.70 (d, *J* = 4.1 Hz, 1H), 4.37 (d, *J* = 9.1 Hz, 1H), 3.93 (s, 3H), 3.35 (s, 3H), 3.29 (s, 1H), 3.18 (dd, *J* = 9.1, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.6, 169.2, 165.9, 163.5, 149.9, 148.3, 146.5, 138.2, 136.0, 133.3, 132.7, 132.0, 130.9, 130.7, 129.8, 128.1, 125.3, 124.3, 120.4, 119.3, 118.2, 117.3, 76.6, 57.5, 53.4, 53.0, 48.5, 42.5. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3401, 1739, 1636, 1534, 1477, 1351, 1257, 1167, 751. HRMS (ESI) for $C_{28}H_{21}Br_2N_2O_{10}$ $[M + H]^+$ calc.: 702.9563; found: 702.9577.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(5-bromo-2-((4-bromobenzoyl)oxy)phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3aea**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-(4-bromobenzoyl)-2*H*-chromen-2-one **1ae** (81.6 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3aea** as a pale yellow solid (140.3 mg, 95%). mp 239.0−239.5 °C. 86% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 10.51 min, t_{major} = 13.05 min). $[\alpha]_D^{25}$ = +23.422 (*c* = 0.5, CH_2Cl_2). R_f: 0.2 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.05 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 1.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.48 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.38 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 5.70 (d, *J* = 7.0 Hz, 1H), 4.36 (d, *J* = 9.0 Hz, 1H), 3.93 (s, 3H), 3.35 (s, 3H), 3.31 (d, *J* = 7.0 Hz, 1H), 3.16 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.6, 169.4, 165.7, 164.7, 150.0, 146.7, 138.0, 133.3, 132.7, 132.0, 131.9, 131.9, 130.9, 129.3, 127.7, 124.5, 120.0, 119.5, 118.2, 117.2, 76.6, 57.7, 53.5, 53.1, 48.5, 42.6. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3401, 3007, 2373, 1745, 1634, 1408, 1277, 1261, 750. HRMS (ESI) for $C_{28}H_{21}Br_3NO_8$ $[M + H]^+$ calc.: 735.8812; found: 735.8809.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(5-bromo-2-((thiophene-2-carbonyl)oxy)phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3aga**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-(thiophene-2-carbonyl)-2*H*-chromen-2-one **1ag** (67.0 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3aga** as a yellow solid (121.1 mg, 91%). mp 175.4−176.1 °C. 87% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 17.46 min, t_{major} = 26.27 min). $[\alpha]_D^{25}$ = +12.231 (*c* = 0.5, CH_2Cl_2). R_f: 0.28 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.01 (d, *J* = 3.3 Hz, 1H), 7.75−7.72 (m, 2H), 7.69 (d, *J* = 4.8 Hz, 1H), 7.46 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.38 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.18 (t, *J* = 4.4 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 5.70 (d, *J* = 6.1 Hz, 1H), 4.36 (d, *J* = 8.9 Hz, 1H), 3.92 (s, 3H), 3.38−3.33 (m, 4H), 3.24 (dd, *J* = 8.9, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.5, 169.5, 165.5, 160.5, 150.0, 146.5, 137.7, 135.3, 134.1, 133.2, 132.6, 131.8, 131.7, 130.9, 128.1, 124.6, 119.8, 119.6, 118.2, 117.0, 76.6, 58.0, 53.4, 53.0, 48.5, 42.7. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3368, 2954, 1771, 1734, 1477, 1413, 1229, 1057. HRMS (ESI) for $C_{26}H_{20}Br_2NO_8S$ $[M + H]^+$ calc.: 663.9276; found: 663.9296.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(5-bromo-2-(cinnamoyloxy)-phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-dicarboxylate (**3aha**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-cinnamoyl-2*H*-chromen-2-one[17] **1ah** (70.8 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3aha** as a white solid (82.0 mg, 60%). mp 145.8−147.0 °C. 80% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 15.41 min, t_{major} = 18.71 min).

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$[\alpha]_D^{25}$ = +6.848 (*c* = 0.5, CH_2Cl_2). R_f: 0.08 (SiO_2, Hexanes: EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 7.88 (d, *J* = 16.0 Hz, 1H), 7.74 (dd, *J* = 7.5, 2.3 Hz, 2H), 7.65−7.60 (m, 2H), 7.49−7.36 (m, 5H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.68 (d, *J* = 16.0 Hz, 1H), 5.70 (s, 1H), 4.34 (d, *J* = 8.9 Hz, 1H), 3.93 (s, 3H), 3.37 (s, 3H), 3.17 (dd, *J* = 8.9, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.6, 169.5, 165.7, 165.3, 150.1, 147.4, 146.7, 137.6, 134.1, 133.3, 132.6, 131.6, 130.8, 130.6, 128.9, 128.5, 124.4, 119.6, 119.4, 118.2, 117.1, 116.5, 57.9, 53.4, 53.1, 48.6, 42.6. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3322, 2364, 1737, 1483, 1353, 1253, 762. HRMS (ESI) for $C_{30}H_{24}Br_2NO_8$ $[M + H]^+$ calc.: 683.9873; found: 683.9869.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(2-((4-methoxybenzoyl)oxy)-phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1-(9bH)-dicarboxylate (**3abb**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-(4-methoxybenzoyl)-2*H*-chromen-2-one[17] **1ab** (71.6 mg, 0.2 mmol), (*E*)-dimethyl 2-((2-hydroxybenzylidene)amino)malonate **2b** (55.3 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3abb** as a white solid (91.6 mg, 75%). mp 228.0−228.1 °C. 72% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 18.21 min, t_{major} = 23.25 min). $[\alpha]_D^{25}$ = +20.231 (*c* = 0.5, CH_2Cl_2). R_f: 0.15 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.17 (d, *J* = 8.5 Hz, 2H), 7.70 (s, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.40−7.27 (m, 3H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 1H), 5.76 (d, *J* = 6.0 Hz, 1H), 4.37 (d, *J* = 8.5 Hz, 1H), 3.89 (s, 6H), 3.36−3.31 (m, 4H), 3.22 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.7, 169.7, 165.8, 165.3, 163.9, 150.1, 147.9, 135.7, 133.2, 132.5, 128.7, 127.4, 126.2, 122.9, 121.3, 119.9, 118.2, 116.9, 113.8, 58.1, 55.4, 53.3, 52.9, 48.6, 42.7. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3430, 2926, 1731, 1637, 1480, 1261, 1165. HRMS (ESI) for $C_{29}H_{25}BrNO_9$ $[M + H]^+$ calc.: 610.0713; found: 610.0713.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(5-methoxy-2-((4-methoxybenzoyl)oxy)phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]-pyrrole-1,1(9bH)-dicarboxylate (**3abc**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-(4-methoxybenzoyl)-2*H*-chromen-2-one[17] **1ab** (71.6 mg, 0.2 mmol), (*E*)-dimethyl 2-((2-hydroxy-5-methoxybenzylidene)amino)malonate **2c** (61.8 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3abc** as a white solid (112.7 mg, 88%). mp 216.0−216.4 °C. 12 % ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 19.35 min, t_{major} = 24.30 min). $[\alpha]_D^{25}$ = −1.928 (*c* = 0.5, CH_2Cl_2). R_f: 0.08 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.15 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.36 (dd, *J* = 6.7, 2.3 Hz, 1H), 7.13 (d, *J* = 3.0 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.88−6.80 (m, 2H), 5.71 (d, *J* = 6.7 Hz, 1H), 4.40 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 6H), 3.84 (s, 3H), 3.37 (d, *J* = 6.7 Hz, 1H), 3.34 (s, 3H), 3.22 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.6, 169.9, 165.7, 165.6, 163.9, 157.5, 150.1, 141.2, 136.6, 133.2, 132.5, 132.4, 123.7, 121.4, 119.9, 118.2, 117.0, 113.8, 112.5, 58.2, 55.5, 55.4, 53.3, 53.0, 48.7, 42.7. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3369, 2954, 1773, 1733, 1607, 1484, 1439, 1262, 1166, 1069. HRMS (ESI) for $C_{30}H_{27}BrNO_{10}$ $[M + H]^+$ calc.: 640.0816; found: 640.0818.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(4-methoxy-2-((4-methoxybenzoyl)oxy)phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]-pyrrole-1,1(9bH)-dicarboxylate (**3abd**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-(4-methoxybenzoyl)-2*H*-chromen-2-one[17] **1ab** (71.6 mg, 0.2 mmol), (*E*)-dimethyl 2-((2-hydroxy-4-methoxybenzylidene)amino)malonate **2d** (61.9 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3abd** as a white solid (87.1 mg, 68%). mp 218.2−220.0 °C. 59% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 18.55 min, t_{major} = 24.68 min). $[\alpha]_D^{25}$ = +5.132 (*c* = 0.5, CH_2Cl_2). R_f: 0.13 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.15 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 2.1 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.35 (dd, *J* = 6.5, 2.2 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.87−6.79 (m, 2H), 6.70 (d, *J* = 2.4 Hz, 1H), 5.65 (s, 1H), 4.35 (d, *J* = 8.8 Hz, 1H), 3.92−3.84 (m, 6H), 3.79 (s, 3H), 3.33 (s, 3H), 3.19 (dd, *J* = 8.8, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.6, 169.7, 165.9, 165.0, 163.9, 159.8, 150.1, 148.6, 133.1, 132.43, 132.39, 128.0, 127.6, 121.3, 119.9, 118.1, 116.8, 113.8, 112.0, 108.5, 76.6, 57.9, 55.5, 55.4, 53.2, 52.8, 48.6, 42.7. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3411, 3024, 2378, 1730, 1632, 1404, 1277, 1261, 1150, 764, 750. HRMS (ESI) for $C_{30}H_{27}BrNO_{10}$ $[M + H]^+$ calc.: 640.0820; found: 640.0818.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(3-methoxy-2-((4-methoxybenzoyl)oxy)phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]-pyrrole-1,1(9bH)-dicarboxylate (**3abe**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-(4-methoxybenzoyl)-2*H*-chromen-2-one[17] **1ab** (71.6 mg, 0.2 mmol), (*E*)-dimethyl 2-((2-hydroxy-3-methoxybenzylidene)amino)malonate **2e** (61.8 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3abe** as a white solid (66.6 mg, 52%). The product is obtained as an inseparable mixture of two diastereomers in a 2:1 ratio. 30% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 22.00 min, t_{major} = 28.34 min). R_f: 0.08 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.17 (d, *J* = 8.5 Hz, 2H (H_a+H_b)), 7.69 (s, 1H (H_a+H_b)), 7.35 (d, *J* = 8.5 Hz, 1H (H_a+H_b)), 7.30−7.21 (m, 1H (H_a+H_b)), 7.20−7.09 (m, 1H (H_a+H_b)), 7.03−6.91 (m, 3H (H_a+H_b)), 6.90−6.75 (m, 1H (H_a+H_b)), 5.83 (s, 1H (H_a)), 5.58 (s, 1H (H_b)), 4.37 (d, *J* = 8.5 Hz, 1H (H_a+H_b)), 3.88 (s, 6H (H_a+H_b)), 3.78 (s, 3H (H_a+H_b)), 3.34 (s, 3H (H_a+H_b)), 3.32−3.10 (m, 1H (H_a+H_b)). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 170.7 (C_a+C_b), 169.7 (C_a+C_b), 165.8 (C_a), 165.0 (C_b), 163.8 (C_a+C_b), 151.5 (C_a+C_b), 150.2 (C_a+C_b), 137.4 (C_a), 137.1 (C_b), 133.2 (C_a+C_b), 132.5 (C_a+C_b), 132.4 (C_a+C_b), 126.5 (C_a+C_b), 121.3 (C_a+C_b), 119.9 (C_a+C_b), 118.5 (C_a), 118.2 (C_b), 116.9 (C_a+C_b), 113.7 (C_a+C_b), 111.6 (C_a+C_b), 76.8 (C_a+C_b), 58.7(C_b), 58.1 (C_a), 56.1 (C_a+C_b), 55.4 (C_a+C_b), 53.3 (C_a+C_b), 52.9 (C_a+C_b), 48.9 (C_b), 48.4 (C_a), 42.9 (C_b), 42.6 (C_a). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3454, 2927, 1729, 1693, 1479, 1259, 692. HRMS (ESI) for $C_{30}H_{27}BrNO_{10}$ $[M + H]^+$ calc.: 640.0814; found: 640.0818.

*(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(3,5-dichloro-2-((4-methoxybenzoyl)oxy)phenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]-pyrrole-1,1(9bH)-dicarboxylate (**3abf**).* Prepared according to the typical procedure **TP-3** using 6-bromo-3-(4-methoxybenzoyl)-2*H*-chromen-2-one[17] **1ab** (71.6 mg, 0.2 mmol), (*E*)-dimethyl 2-((3,5-dichloro-2-hydroxybenzylidene)amino)malonate **2f** (70.2 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **3abf** as a white solid (40.8 mg, 30%). The product is obtained as an inseparable mixture of two diastereomers in a 3:2 ratio. 14 % ee determined by HPLC on Chiralpak IB column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 17.53 min, t_{major} = 32.54 min). R_f: 0.15 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.14 (d, *J* = 8.4 Hz, 2H (H_a+H_b)), 7.72 (s, 1H (H_a+H_b)), 7.60−7.48 (m, 1H (H_a+H_b)), 7.46−7.33 (m, 2H (H_a+H_b)), 7.05−6.94 (m, 2H (H_a+H_b)), 6.90−6.77 (m, 1H (H_a+H_b)), 5.76 (d, *J* = 6.8 Hz, 1H (H_a)), 5.52 (d, *J* = 6.8 Hz, 1H (H_b)), 4.36 (d, *J* = 8.8 Hz, 1H (H_a)), 4.27 (d, *J* = 8.8 Hz, 1H (H_b)), 3.96−3.85 (m, 6H (H_a+H_b)), 3.40−3.33 (m, 4H (H_a+H_b)), 3.29 (d, *J* = 9.6 Hz, 1H (H_b)), 3.19 (d, *J* = 9.6 Hz, 1H (H_a)). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 170.5 (C_a), 170.3 (C_b), 169.5 (C_b), 169.2 (C_a), 165.6 (C_a), 165.1 (C_b), 164.5 (C_a), 164.2 (C_a+C_b), 163.4 (C_b), 150.1 (C_a+C_b), 143.4 (C_a), 143.3 (C_b), 140.1 (C_a), 139.7 (C_b), 133.2 (C_a+C_b), 132.7 (C_a+C_b), 132.0 (C_a+C_b), 129.0 (C_a), 128.8 (C_b), 126.4 (C_b), 126.3 (C_a), 120.4 (C_a), 120.3 (C_b), 119.5 (C_b), 119.4 (C_a), 118.2 (C_a), 117.1 (C_b), 113.9 (C_a+C_b), 76.6 (C_a), 76.5 (C_b), 58.7 (C_b), 57.7 (C_a), 55.4 (C_a+C_b), 53.4 (C_b), 53.0 (C_a), 48.6 (C_b), 47.9 (C_a), 42.8 (C_b), 42.4 (C_a). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3429, 2956, 1735, 1610, 1476, 1261, 756. HRMS (ESI) for $C_{29}H_{23}BrCl_2NO_9$ $[M + H]^+$ calc.: 677.9938; found: 677.9933.

(3R,3aR,9bR)-Dimethyl 8-Bromo-3-(5-bromo-2-hydroxyphenyl)-4-oxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1(9bH)-

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*dicarboxylate (**4aia**).* Prepared according to the typical procedure **TP-3** using 6-bromo-2-oxo-2*H*-chromene-3-carboxylic acid[20a] **1ai** (53.8 mg, 0.2 mmol) or methyl 6-bromo-2-oxo-2*H*-chromene-3-carboxylate[20b] **1aj** (56.6 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). (Reaction was maintained at 30 °C when **1aj** was used). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **4aia** as a white solid (65.2 mg, 59% from **1ai** or 38.7 mg, 35% from **1aj**). mp 82.7−83.6 °C. 20% ee from **1ai** and 9% ee from **1aj** as determined by HPLC on Chiralpak AD-H column (hexane/IPA = 80/20, flow rate = 1.0 mL/min, t_{minor} = 15.25 min, t_{major} = 28.13 min). $[\alpha]_D^{25}$ = +0.192 (*c* = 0.5, CH_2Cl_2) from **1ai** and $[\alpha]_D^{25}$ = +0.028 (*c* = 0.5, CH_2Cl_2) from **1aj**. R_f: 0.07 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 9.90 (brs, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.44 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.40 (d, *J* = 2.3 Hz, 1H), 7.26 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 5.53 (d, *J* = 2.8 Hz, 1H), 4.41 (d, *J* = 9.7 Hz, 1H), 3.89 (s, 3H), 3.45−3.41 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 169.5, 168.4, 167.2, 155.6, 149.9, 133.4, 133.0, 132.3, 129.9, 126.0, 119.6, 118.7, 118.6, 117.4, 111.9, 76.2, 62.0, 53.7, 53.7, 48.4, 43.9. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3461, 2825, 2071, 1681, 1416, 703. HRMS (ESI) for $C_{21}H_{17}Br_2NO_7$ $[M + H]^+$ calc.: 553.9450; found: 553.9454.

*(3R,3aR,9bR)-Dimethyl 3-(2-(Benzoyloxy)-5-bromophenyl)-8-bromo-4-thioxo-2,3,3a,4-tetrahydrochromeno[3,4-c]pyrrole-1,1-(9bH)-dicarboxylate (**8aaa**).* Prepared according to the typical procedure **TP-3** using (6-bromo-2-thioxo-2*H*-chromen-3-yl)(phenyl)-methanone[21] **7aa** (68.7 mg, 0.2 mmol), (*E*)-dimethyl 2-((5-bromo-2-hydroxybenzylidene)amino)malonate **2a** (72.6 mg, 1.1 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL). Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **8aaa** as a white solid (94.3 mg, 70%). mp 230.2−231.4 °C. 91% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 95/5, flow rate = 1.0 mL/min, t_{minor} = 16.57 min, t_{major} = 19.53 min). $[\alpha]_D^{25}$ = −18.762 (*c* = 0.5, CH_2Cl_2). R_f: 0.21 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.15 (d, *J* = 7.4 Hz, 2H), 7.71 (dd, *J* = 7.4, 2.6 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52−7.45 (m, 3H), 7.41 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.01 (d, *J* = 8.5, 2.6 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.08 (s, 1H), 4.31 (d, *J* = 8.5 Hz, 1H), 3.95 (s, 3H), 3.31 (s, 3H), 3.20 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 209.7, 170.2, 170.0, 165.2, 150.0, 147.0, 137.8, 133.3, 132.6, 131.7, 131.4, 130.5, 128.7, 128.6, 124.6, 120.4, 119.8, 117.8, 117.6, 76.4, 63.2, 56.8, 53.6, 53.1, 41.5. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3410, 3002, 1732, 1629, 1401, 1276, 1261, 1035, 750.35. HRMS (ESI) for $C_{28}H_{22}Br_2NO_7S$ $[M + H]^+$ calc.: 673.9485; found: 673.9484.

*(1S,3R,3aR,9bR)-Methyl 3-(2-(Benzoyloxy)-5-bromophenyl)-8-bromo-1-methyl-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]-pyrrole-1-carboxylate (**6aa**).* Prepared according to the typical procedure **TP-3** using 3-benzoyl-6-bromo-2*H*-chromen-2-one[16] **1aa** (65.8 mg, 0.2 mmol), (*E*)-methyl 2-((5-bromo-2-hydroxybenzyl-idene)amino)propanoate[22] **5** (74.1 mg, 1.3 equiv), and quinidine (13.2 mg, 20 mol %) in NMP (1.0 mL) at −30 °C. Purification by flash chromatography (SiO_2, EtOAc:Hexanes, 1:3) furnished the desired product **6aa** as a white solid (96.8 mg, 79%, diastereomeric ratio = 9:1). mp 229.1−230.7 °C. 70% ee determined by HPLC on Chiralpak IB column (hexane/IPA = 95/5, flow rate = 1.0 mL/min, t_{minor} = 16.57 min, t_{major} = 19.53 min). $[\alpha]_D^{25}$ = +9.512 (*c* = 0.5, CH_2Cl_2). R_f: 0.21 (SiO_2, Hexanes:EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm 8.18 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 2.6 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.54−7.48 (m, 3H), 7.45 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.03 (d, *J* = 8.4, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.50 (s, 1H), 4.06 (d, *J* = 9.3 Hz, 1H), 3.90 (s, 3H), 3.18 (dd, *J* = 8.8, 1.6 Hz, 1H), 1.05(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm 174.6, 167.4, 165.2, 150.6, 146.9, 138.2, 134.0, 132.7, 132.2, 131.6, 131.2, 130.4, 128.7, 124.6, 121.1, 118.5, 117.3, 69.2, 57.1, 52.9, 48.5, 43.4, 22.0. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3410, 3024, 1730, 1631, 1403, 1276, 1261, 1150. HRMS (ESI) for $C_{27}H_{22}Br_2NO_6$ $[M + H]^+$ calc.: 613.9814; found: 613.9816.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02041.

Copies of ^{1}H, ^{13}C NMR spectra for all new compounds and HPLC chromatograms for appropriate compounds (PDF)

X-ray crystallographic data for compound **8aaa** (CIF)

X-ray crystallographic data for compound **6aa** (CIF)

X-ray crystallographic data for compound **3aba** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: +886-2-77346131. E-mail: wenweilin@ntnu.edu.tw.

Author Contributions

†These authors made equal contributions to this work.

Notes

The authors declare no competing financial interest.

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