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Enantioselective Synthesis of Spiropyrazolone-Fused Cyclopenta[*c*]chromen-4-ones Bearing Five Contiguous Stereocenters via (3+2) Cycloaddition

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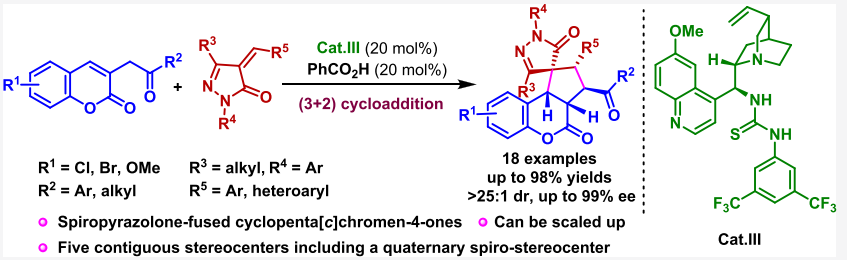

ABSTRACT: An enantioselective synthesis of spiropyrazolone-fused cyclopenta[*c*]chromen-4-ones is demonstrated via a (3+2) cycloaddition reaction. The reactions of 3-homoacylcoumarins and α,β-unsaturated pyrazolones in the presence of the cinchona-alkaloid derived hydrogen-bonding catalyst provide aforementioned spiropyrazolone-chromenone adducts bearing five contiguous stereocenters, of which one is the spiro all-carbon quaternary stereocenter in high yields (up to 98%) with good to excellent stereoselectivities (>25:1 dr and up to 99% ee). This one-pot methodology could also be practically demonstrated on a gram-scale with similar efficacy.

Pyrazolones are important structural motifs that are widely found in natural products and medicinally important compounds exhibiting a wide range of biological and pharmacological activities.[1] Specifically, 4-spiro-5-pyrazolones have emerged as promising pharmacophores in medicinal chemistry.[2] Consequently, significant efforts have been focused on the catalytic asymmetric synthesis of chiral spiro six-membered rings over the past few decades.[3] However, the methods to construct spiro five-membered ring bearing spiro-pyrazolones were rarely explored.[4] On the other hand, coumarin derivatives are privileged heterocyclic scaffolds in medicinal and materials science; recently, they have attracted more attention from synthetic chemists because of their utility for the construction of complex structures and bioactive skeletons.[5] In particular, cyclopentane-fused coumarin derivatives are important scaffolds found in many alkaloids and sesquiterpenes.[6] Owing to their medicinal properties (Figure 1),[7] the development of methods to construct new fused-ring tetracyclic frameworks of these systems would have shown more potentiality in the area of drug discovery.

Earlier, our group developed a new type of all-carbon 1,3-dipolar precursor such as 3-homoacylcoumarin, and it was utilized to prepare a series of five-membered coumarin-fused spirocyclopentanes in high yields and excellent stereoselectivities via the (3+2) cycloaddition reaction.[8] In continuation of our effort toward the exploration of organocatalytic cascade reactions to construct the complex molecular architectures,[9] we were interested in developing a (3+2) cycloaddition reaction for the synthesis of spiropyrazolones, using 3-homoacylcoumarins and α,β-unsaturated pyrazolones. This asymmetric methodology would access the hybrid chiral complex skeletons bearing five contiguous stereocenters including a quaternary stereogenic center at the C-4 position of pyrazolones. Herein, we report a method for the enantioselective construction of spiropyrazolone-fused cyclopenta[*c*]chromen-4-ones in high yields and good to excellent enantioselectivities via a (3+2) cycloaddition reaction (Scheme 1).

We started our investigation to examine a model reaction between 3-homoacylcoumarin **1a** and α,β-unsaturated pyrazolone **2a** with 20 mol % of 1,4-diazabicyclo[2.2.2]octane (DABCO) in CH_2Cl_2 at 30 °C. Delightfully, the spiropyrazolone-fused cyclopenta[*c*]chromen-4-one derivative **3aa** was successfully produced in 99% yield after 16 h (entry 1, Table 1). The result from the racemic version enforced us to screen different tertiary amine hydrogen bond donor bifunctional

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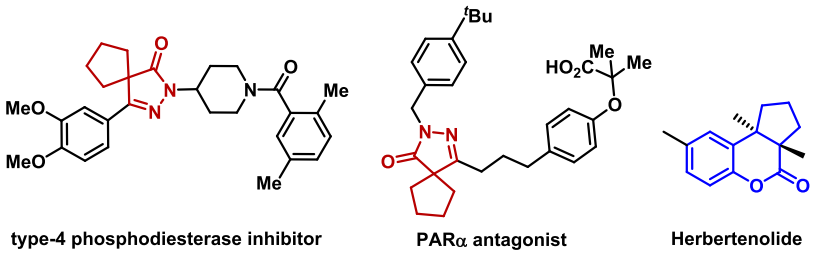


Figure 1. Selected biological active spiropyrazolones and coumarin-fused cyclopentanes.

Scheme 1. Design for the Construction of Spiropyrazolone-Fused Cyclopenta[*c*]chromen-4-ones via (3+2) Cycloaddition

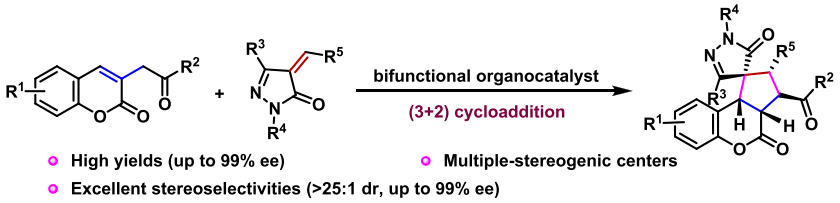
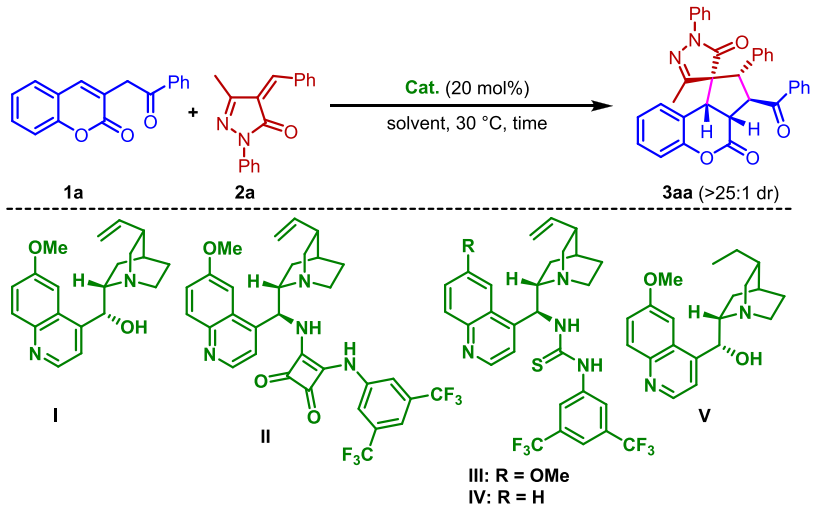


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	*t* (h)	**3aa** (%)[b]	ee (%)[c]
1	DABCO	CH_2Cl_2	16	99	racemic
2	**I**	CH_2Cl_2	24	99	53
3	**II**	CH_2Cl_2	22	53	68
4	**III**	CH_2Cl_2	24	91	71
5	**IV**	CH_2Cl_2	18	84	70
6	**V**	CH_2Cl_2	15	92	37
7	**III**	THF	24	73	61
8	**III**	DCE	24	93	71
9	**III**	CH_3CN	16	98	15
10	**III**	toluene	16	86	75
11	**III**	*o*-xylene	16	84	75
12[d]	**III**	toluene	72	92	87
13[d,e]	**III**	toluene	192	85	87
14[d,f]	**III**	toluene	36	95	75
15[d,g]	**III**	toluene	72	96	87
16[d,h]	**III**	toluene	72	97	85

[a]Unless otherwise specified, all reactions were carried out with **1a** (0.2 mmol, 1.0 equiv), **2a** (0.2 mmol, 1.0 equiv), and catalyst (20 mol %) in a given solvent (1.0 mL) at 30 °C. [b]The yield of the product **3aa** was determined by ^{1}H NMR analysis using Ph_3CH as an internal standard. [c]Enantiomeric excess was determined by chiral HPLC analysis. [d]Benzoic acid (20 mol %) was used. [e]Catalyst **III** (10 mol %) was used. [f]Toluene (0.5 mL) was used. [g]1.1 equiv of **2a** was used. [h]1.2 equiv of **2a** was used.

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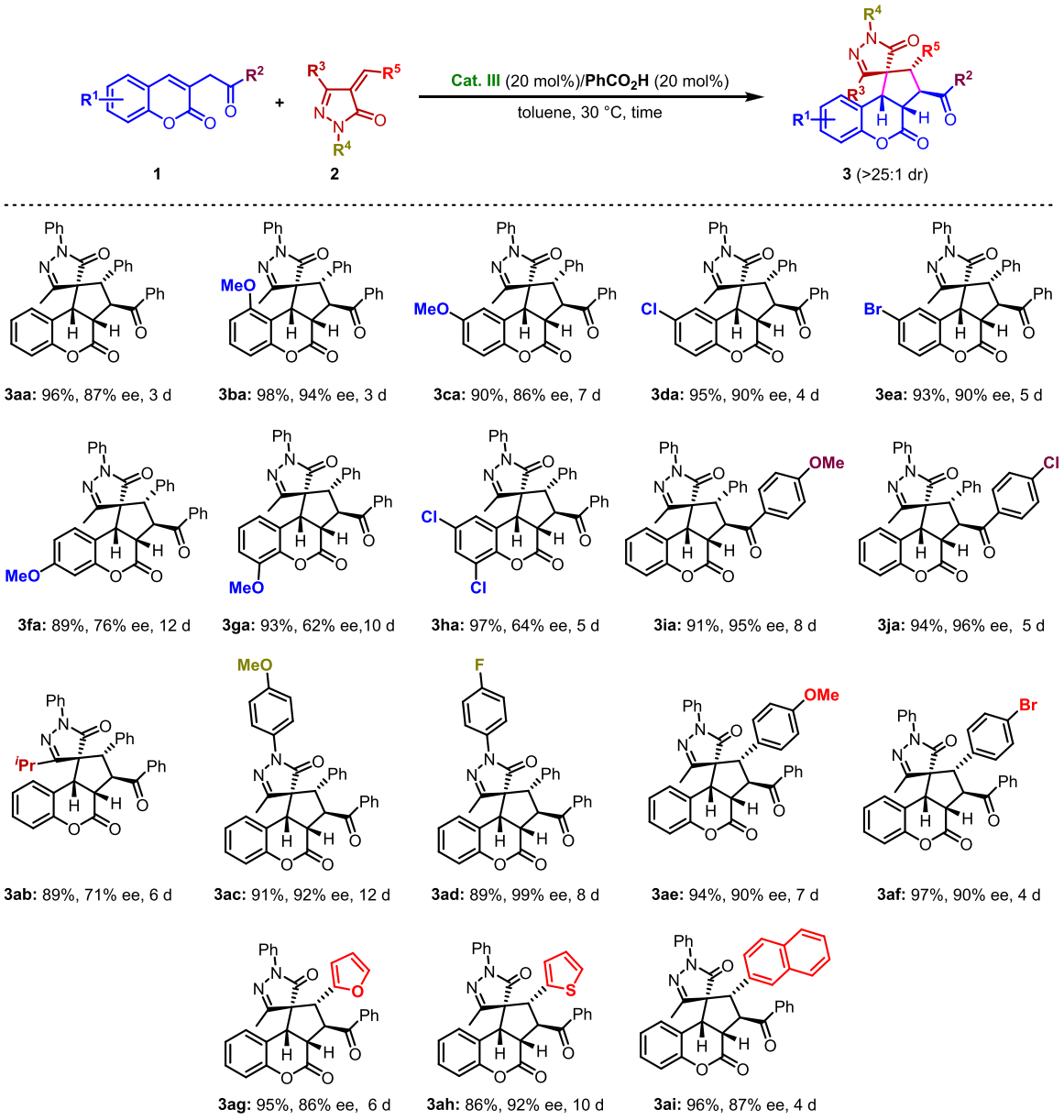
Scheme 2. Substrate Scope of the (3+2) Cycloaddition Reaction[a,b,c]



[a]Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol), **2** (1.1 equiv), benzoic acid (20 mol %), and catalyst **III** (20 mol %) in toluene (1.0 mL) at 30 °C. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

organocatalysts for the optimal reaction conditions of an asymmetric (3+2) cycloaddition reaction.

Accordingly, the effect of commercially available catalyst **I** was examined in CH_2Cl_2 at 30 °C. The spiropyrazolone-fused cyclopenta[*c*]chromen-4-one derivative **3aa** was obtained in excellent yield (99%) with moderate enantioselectivity (53% ee) within 24 h (entry 2). To improve the enantioselectivity of the product, other catalysts were evaluated (entries 3−6, see Supporting Information for detailed optimization). Among them, the thiourea derivative **III** was selected as the better catalyst for the (3+2) cycloaddition reaction to afford the desired product **3aa** in 91% yield with 71% enantioselectivity (entry 4). Next, various solvents such as THF, 1,2-dichloroethane (DCE), MeCN, toluene, and *o*-xylene were screened (entries 7−11). Gratefully, toluene was found to be a suitable solvent in terms of both yield and enantioselectivity, providing a (3+2) cycloaddition product **3aa** in 86% yield and 75% ee within 16 h (entry 10). Under the same conditions, the use of $PhCO_2H$ as the additive uplifted the yield and selectivity of the product **3aa** to 92% yield and 87% ee, albeit after a longer reaction time (entry 12). It is worthy to note that, in all cases, excellent diastereoselectivity of **3aa** was found (>25:1 dr). Furthermore, we attempted to investigate other reaction parameters, such as catalyst loading, the concentration of the reaction, and equivalents of substrates. It should be noticed that decreasing the catalyst loading to 10 mol % resulted in a lower yield of **3aa** to 85%, but the enantioselectivity was retained as 87% ee (entry 13). Finally, increasing the ratio of substrate **2a** improved the yield of the product **3aa** up to 97% (entries 15 and 16). Thus, the optimal conditions for **3aa** were established with **1a** (0.2 mmol), **2a** (1.1 equiv), catalyst **III** (20

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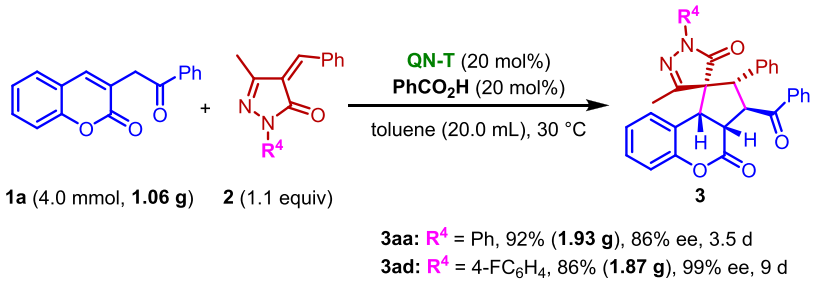
Scheme 3. Gram-Scale Reactions for the Synthesis of Spiropyrazolones 3aa and 3ad



1a (4.0 mmol, **1.06 g**) **2** (1.1 equiv) **3**

3aa: R^4 = Ph, 92% (**1.93 g**), 86% ee, 3.5 d
3ad: R^4 = 4-FC_6H_4, 86% (**1.87 g**), 99% ee, 9 d

mol %), and $PhCO_2H$ (20 mol %) in toluene (1.0 mL) at 30 °C as shown in entry 15.

Once the optimal reaction conditions were established (Table 1, entry 15), the scope and generality of the (3+2) cycloaddition reaction with the variety of reactants **1** and **2** were investigated (Scheme 2). At first, the scope of 3-homoacylcoumarin **1** bearing various R^1 and R^2 substituents was tested. The substrate **1** with different R^1 substitutions reacted smoothly with **2a** to afford the products **3aa**−**3ha** in high yields and good enantioselectivities (up to 98% and 94% ee), regardless of the electronic nature of the substituent. When the substrate contains the OMe (R^1) group at different positions (**3ba**, **3ca** and **3fa**, **3ga**), the significant positional effect was found in the reaction outcome in terms of enantioselectivities, but the excellent yields were maintained. Notably, substrate **1h** bearing a 6,8-dichloro substituent also furnished the desired product **3ha** in 97% yield, albeit providing only moderate enantioselectivity. Furthermore, the 3-homoacylcoumarin with different R^2 substituents **1i** and **1j** also reacted well with **2a** to provide the spiropyrazolone derivatives **3ia** and **3ja** in 91% and 94% yields and 95% and 96% enantioselectivities, respectively. We have also tested the substrate bearing R^2 as an aliphatic CH_3 group with **2a**, but the corresponding product could not be found in the reaction, even prolonging the reaction time up to 24 h.

Next, we turned our attention toward the substitution effect of *α,β*-unsaturated pyrazolones **2** bearing different R^3, R^4, and R^5 groups to test with 3-homoacylcoumarin **1a**. The substrate **2b** containing the ^{i}Pr group as an R^3 substitution afforded the corresponding product **3ab** in 89% yield with moderate enantioselectivity. Furthermore, the effect of various R^4 substituents on amide functionality was also investigated. It was delightful to find that the corresponding products **3ac** and **3ad** were obtained in high yields and excellent enantioselectivities (up to 99% ee), irrespective of the electronic nature of the substituent. Finally, substrates with different R^5 groups were also tested under the standard reaction conditions. All substrates were well-tolerated to afford the corresponding products **3ae**−**3ai** in good yields and enantioselectivities. Interestingly, the substrates **2g** and **2h** bearing heteroaryl (R^5 = 2-furyl and 2-thienyl) substituents also furnished the desired products **3ag** and **3ah** in up to 95% yields with up to 92% ee. It is worth noting that the sterically hindered substrate **2i** (R^5 = 2-naphthyl) also smoothly reacted with **1a** to provide the spiropyrazolone derivative **3ai** in excellent yield and good enantioselectivity. We have also attempted to prepare substrate **2** bearing R^4 and R^5 as an aliphatic group, to test in the reaction with **1a** under our standard conditions. Unfortunately, our efforts to prepare the substrate **2** bearing R^4 and R^5 as an aliphatic group such as methyl, ethyl, or ^{t}butyl were unsuccessful.

To demonstrate the synthetic utility of our protocol, we selected two substrates of *α,β*-unsaturated pyrazolones **2** for the gram-scale reactions with 3-homoacylcoumarin **1a**. Both substrates **2a** and **2d** furnished the desired spiropyrazolone-fused cyclopenta[*c*]chromen-4-one derivatives **3aa** and **3ad** in up to 92% yields and 99% ee with similar efficacy in substantial quantities under the standard conditions (Scheme 3).

The absolute stereochemistry of spiropyrazolone-fused cyclopenta[*c*]chromen-4-one derivative **3ea** was assigned unambiguously by single-crystal X-ray diffraction analysis and that of the other derivatives were assigned by analogy.[10] The ORTEP diagram for **3ea** was shown in Figure 2.

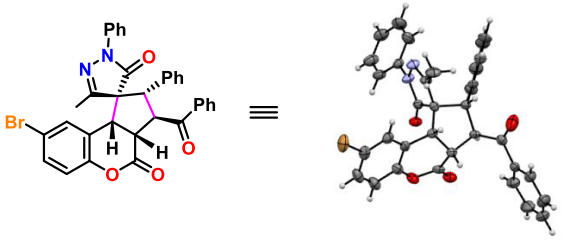


Figure 2. ORTEP diagram of **3ea** (CCDC 1992666).

Furthermore, to demonstrate the reaction pathway, we have carried out several control experiments at lower reaction temperatures (0 °C to −10 °C), and the progress of the reactions was monitored by ^{1}H NMR analysis. However, we could not find the Michael adduct intermediate in any of the reactions. On the basis of our previous reports,[8] we imagined that Michael−Michael addition may be less efficient, and the reaction more likely proceeds through a (3+2) cycloaddition. It was also noticed that the reaction was promoted effectively by the combined use of a bifunctional thiourea catalyst with a Brønsted acid as an additive. Eventually, the formation of possible intermediates or transition states had a different fate under the addition of the additive and thus significantly improved the yields and enantioselectivities of the formation of products, although the acid additive showed no effects in enantioselectivities of products in our previous studies.[8,9b] Therefore, we assume that the double activation of both the substrates through hydrogen bond involvements may be possible for the reaction mechanism.

Based on analyzing the experimental data, the screening of catalysts, and the absolute configurations of the products, a stereochemical model for the (3+2) cycloaddition reaction is depicted in Figure 3. The significance of catalyst **III** to achieve the high enantioselectivities in the (3+2) cycloaddition asserts the possibility of the proposed model. Furthermore, the role of the thiourea-derivatization of the cinchona catalyst for a

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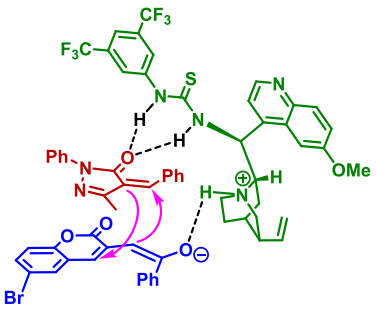

Figure 3. Stereochemical model for (3+2) cycloaddition of 3-homoacylcoumarin **1e** and α,β-unsaturated pyrazolone **2a**.

hydrogen-bond donor is crucial to afford the desired products with high stereoselectivities (Table 1, entries 2−6).

In conclusion, we have developed an efficient protocol for the construction of highly stereoselective spiropyrazolone-fused cyclopenta[*c*]chromen-4-ones from 3-homoacylcoumarins and α,β-unsaturated pyrazolones catalyzed by a cinchona-based chiral amine catalyst via a (3+2) cycloaddition reaction. The cascade products are obtained in high yields with excellent diastreo and enantioselectivities under mild and one-pot reaction conditions. In addition, the reaction could also be performed on a gram scale with similar efficacy. Further exploration of the substrate scope of this catalytic system and the biological evaluations of the resulting spiro compounds are in progress in our laboratory.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven-dried glassware with a magnetic stir bar. Unless otherwise stated, all reagents were used as purchased from commercial suppliers without further purification. Analytical thin-layer chromatography (TLC) was performed on precoated, alumina-backed silica gel plates (Merck 60 F254, 0.2 mm thickness), which were developed using UV irradiation at 254 nm. Flash column chromatography was performed using silica gel (Silicycle SiliaFlash P60, 230−400 mesh). Melting points were measured on a Fargo melting point apparatus and were uncorrected. IR spectra were recorded on a PerkinElmer 500 spectrometer, and only selected peaks were mentioned. ^{1}H NMR spectra were recorded on either a Bruker AV-400 spectrometer or a Bruker AV-III HD-400 spectrometer. Chemical shifts were reported in δ ppm and referenced to the following internal standards: TMS (δ = 0.00 ppm for ^{1}H NMR), chloroform-*d* (δ = 77.00 ppm for ^{13}C NMR), and DMSO-d_6 (δ = 2.50 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR). The following abbreviations (or any combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, td = triplet of doublet, qd = quartet of doublet, pt = pseudo triplet, br = broad. High-resolution mass spectra were recorded on a JEOL MStation JMS-700 (2) using EI (Magnetic sector analyzer) or on a Waters Xevo G2-S Tof using ESI (TOF analyzer). The X-ray diffraction measurements were carried out at 200 K on a Bruker KAPPA APEX II 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 CH_2Cl_2 on a Polarimeter with a 50 mm cell (c given in g/100 mL) operated at λ = 589 nm, corresponding to the sodium D line, at the indicated temperatures.

Experimental Procedures. *General Procedure for the Preparation of Starting Materials* **1**.[8,9b,11] A round-bottomed flask equipped with a magnetic stir bar was charged with lactone derivative (1.0 mmol), salicylaldehyde derivative (1.1 equiv), Et_3N (1.0 mL), and CH_2Cl_2 (30.0 mL), and the mixture was stirred at 30 °C in a water bath. After the completion of the reaction as monitored by TLC, the reaction mixture was quenched with 1 M HCl, extracted with CH_2Cl_2, and washed with brine. The combined organic layers were then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was recrystallized from ethanol to give pure 3-homoacylcoumarin **1**.

General Procedure for the Preparation of Starting Materials **2**.[12] A round-bottomed flask equipped with a magnetic stir bar was charged with *b*-keto ethyl ester derivative (10.0 mmol), and hydrazine derivative (1.1 equiv) in acetic acid (20.0 mL) was refluxed for 6−8 h in an oil bath. After the completion of the reaction, the crude mixture was left to cool. The crude pyrazolone product was obtained by recrystallization from acetic acid as a yellow solid and directly subjected to the next step without further purification. To a solution of crude pyrazolone (8.0 mmol) in acetic acid (20.0 mL) were added aldehyde (1.1 equiv) and sodium acetate (1.1 equiv). The mixture was stirred at 30 °C for 1−3 h. After the completion of the reaction, H_2O (50 mL) was added to the reaction mixture, and the aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was further subjected to flash column chromatography (hexanes/EtOAc = 10:1 as an eluent) to afford pure α,β-unsaturated pyrazolone derivative **2**.

Typical Procedure for the Synthesis of Spiropyrazolone-Fused Cyclopenta[c]chromen-4-ones **3**. A capped glass vial equipped with a magnetic stir bar was charged with **1** (0.2 mmol), **2** (1.1 equiv), catalyst **III** (20 mol %), and benzoic acid (20 mol %) in toluene (1.0 mL), and the mixture was stirred at 30 °C in a water bath. The progress of the reaction was monitored by TLC analysis and ^{1}H NMR data analysis until the complete consumption of 3-homoacylcoumarin **1**. After the reaction was complete, the solvent was removed under reduced pressure. The crude residue was subjected by column chromatography over silica gel (hexanes/EtOAc as an eluent) to afford pure product **3**.

*(1R,2S,3R,3aR,9bR)-3-Benzoyl-3′-methyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3aa**).* Following the typical procedure, **3aa** was obtained from **1a** (52.9 mg, 0.2 mmol) and **2a** (57.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 3 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3aa** as a white solid (101.1 mg, 96%). Mp: 221.8−222.2 °C. R_f = 0.25 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +150.43 (c = 0.25 in CH_2Cl_2). HPLC: 87% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 21.36 min (major), 18.84 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.08 (d, J = 7.5 Hz, 2H), 7.49 (t, J = 7.5 Hz, 1H), 7.41−7.30 (m, 4H), 7.28 (d, J = 7.5 Hz, 2H), 7.25−7.08 (m, 6H), 7.08−6.96 (m, 3H), 6.91 (d, J = 7.7 Hz, 1H), 5.63 (dd, J = 10.2, 4.4 Hz, 1H), 4.13 (d, J = 10.6 Hz, 1H), 4.07 (d, J = 10.2 Hz, 1H), 3.83 (dd, J = 10.6, 4.4 Hz, 1H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.5, 172.3, 167.4, 157.6, 151.2, 136.7, 135.9, 134.0, 133.8, 129.9, 129.3, 128.8, 128.5, 128.4, 128.1, 127.3, 125.4, 124.3, 119.4, 117.8, 116.2, 72.2, 56.1, 52.7, 46.0, 44.3, 13.8. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3061, 1637, 1456, 1373, 1312, 1279, 1237, 703. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{34}H_{27}N_2O_4$, 527.1969; found, 527.1971.

*(1R,2S,3R,3aR,9bR)-3-Benzoyl-9-methoxy-3′-methyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3ba**).* Following the typical procedure, **3ba** was obtained from **1b** (60.1 mg, 0.2 mmol) and **2a** (57.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 3 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ba** as a white solid (109.1 mg, 98%). Mp: 207.5−208.6 °C. R_f = 0.20 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +259.60 (c = 0.25 in CH_2Cl_2). HPLC: 94% ee, (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 21.65 min (major), 18.93 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.04 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.35−7.26 (m, 4H), 7.20−7.05 (m, 6H), 7.02 (t, J = 7.5 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 6.50 (d, J = 8.5 Hz, 1H), 5.54 (dd, J = 10.2, 4.0 Hz, 1H), 4.30 (d, J = 10.6 Hz, 1H), 4.09 (d, J = 10.2 Hz, 1H), 3.75 (s, 3H), 3.72 (dd, J = 10.6, 4.0 Hz, 1H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25

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°C) δ/ppm: 201.2, 172.4, 167.7, 159.8, 157.1, 152.3, 137.0, 135.8, 134.4, 133.6, 130.1, 129.2, 128.7, 128.4, 128.2, 128.1, 125.0, 119.1, 110.1, 105.8, 71.1, 56.1, 55.0, 52.9, 44.7, 42.2, 14.1. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2919, 2853, 1756, 1643, 1500, 1367, 1239, 1160, 751. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{35}H_{29}N_2O_5$, 557.2075; found, 557.2076.

*(1R,2S,3R,3aR,9bR)-3-Benzoyl-8-methoxy-3′-methyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3ca**).* Following the typical procedure, **3ca** was obtained from **1c** (60.1 mg, 0.2 mmol) and **2a** (57.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 7 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ca** as a white solid (100.2 mg, 90%). Mp: 221.1−221.6 °C. R_f = 0.10 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +206.93 (*c* = 0.25 in CH_2Cl_2). HPLC: 86% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 32.40 min (major), 24.68 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.07 (dd, *J* = 7.9 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 2H), 7.14−6.99 (m, 4H), 6.96 (d, *J* = 8.8 Hz, 1H), 6.72 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.40 (d, *J* = 2.8 Hz, 1H), 5.62 (dd, *J* = 10.2, 4.4 Hz, 1H), 4.08 (d, *J* = 10.6 Hz, 1H), 4.05 (d, *J* = 10.2 Hz, 1H), 3.79 (dd, *J* = 10.6, 4.3 Hz, 1H), 3.66 (s, 3H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.5, 172.2, 167.6, 157.5, 155.7, 145.1, 136.8, 135.9, 133.9, 133.7, 129.2, 128.7, 128.5, 128.4, 128.3, 128.0, 125.2, 119.2, 118.4, 116.9, 114.7, 112.5, 72.1, 56.1, 55.5, 52.5, 46.0, 44.0, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2972, 2834, 1639, 1498, 1377, 1295, 1090, 700. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{35}H_{29}N_2O_5$, 557.2075; found, 557.2076.

*(1R,2S,3R,3aR,9bR)-3-Benzoyl-8-chloro-3′-methyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3da**).* Following the typical procedure, **3da** was obtained from **1d** (61.2 mg, 0.2 mmol) and **2a** (57.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 4 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3da** as yellow solid (106.6 mg, 95%). Mp: 208.7−209.1 °C. R_f = 0.25 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +114.11 (*c* = 0.25 in CH_2Cl_2). HPLC: 90% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 21.09 min (major), 17.37 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.05 (d, *J* = 8.4 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.39−7.31 (m, 4H), 7.30−7.25 (m, 2H), 7.24−7.03 (m, 7H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 5.60 (dd, *J* = 10.2, 4.2 Hz, 1H), 4.06 (d, *J* = 10.8 Hz, 1H), 4.03 (d, *J* = 10.2 Hz, 1H), 3.82 (dd, *J* = 10.8, 4.2 Hz, 1H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.3, 172.1, 166.9, 157.2, 149.8, 136.6, 135.7, 133.9, 133.7, 130.1, 129.3, 128.9, 128.6, 128.5, 128.0, 127.0, 125.6, 119.3, 119.2, 117.9, 72.1, 56.2, 52.5, 45.5, 44.0, 13.8. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3078, 1759, 1640, 1486, 1375, 1307, 1238, 1159, 1090, 749, 689. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{35}ClN_2O_4$ 561.1578; found, 561.1581. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{37}ClN_2O_4$, 563.1567; found, 563.1552.

*(1R,2S,3R,3aR,9bR)-3-Benzoyl-8-bromo-3′-methyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3ea**).* Following the typical procedure, **3ea** was obtained from **1e** (70.0 mg, 0.2 mmol) and **2a** (57.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 5 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ea** as a white solid (112.6 mg, 93%). Mp: 212.6−213.2 °C. R_f = 0.35 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +214.45 (*c* = 0.25 in CH_2Cl_2). HPLC: 90% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 19.85 min (major), 16.64 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.05 (d, *J* = 8.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.42−7.25 (m, 7H), 7.21 (t, *J* = 8.0 Hz, 2H), 7.17−7.03 (m, 4H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 5.60 (dd, *J* = 10.2, 4.2 Hz, 1H), 4.06 (d, *J* = 10.8 Hz, 1H), 4.03 (d, *J* = 10.2 Hz, 1H), 3.82 (dd, *J* = 10.8, 4.2 Hz, 1H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.3, 172.1, 166.8, 157.2, 150.4, 136.6, 135.8, 133.9, 133.7, 133.0, 130.0, 129.3, 128.8, 128.6, 128.54, 128.52, 128.0, 125.6, 119.6, 119.4, 118.4, 116.6, 72.1, 56.2, 52.6, 45.4, 44.0, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2923, 2848, 1752, 1639, 1483, 1369, 1336, 1215, 1077, 751, 667. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{79}BrN_2O_4$ 605.1077; found, 605.1076. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{81}BrN_2O_4$, 607.1064; found, 607.1050.

*(1R,2S,3R,3aR,9bR)-3-Benzoyl-7-methoxy-3′-methyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3fa**).* Following the typical procedure, **3fa** was obtained from **1f** (60.1 mg, 0.2 mmol) and **2a** (57.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 12 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3fa** as a white solid (99.1 mg, 89%). Mp: 180.7−181.4 °C. R_f = 0.15 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +214.45 (*c* = 0.25 in CH_2Cl_2). HPLC: 76% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 22.99 min (major), 25.02 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.08 (d, *J* = 8.5 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.41−7.31 (m, 4H), 7.31−7.25 (m, 2H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.15−6.99 (m, 4H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.60−6.50 (m, 2H), 5.61 (dd, *J* = 10.2, 4.3 Hz, 1H), 4.08 (d, *J* = 10.8 Hz, 1H), 4.05 (d, *J* = 10.2 Hz, 1H), 3.79 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.68 (s, 3H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.5, 172.4, 167.5, 160.5, 157.7, 152.1, 136.8, 135.9, 134.1, 133.7, 129.2, 128.7, 128.5, 128.4, 128.3, 128.0, 125.3, 119.2, 111.2, 107.9, 102.4, 72.1, 56.0, 55.4, 52.5, 45.5, 44.3, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2988, 2857, 1637, 1498, 1275, 1155, 1073, 685. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{35}H_{29}N_2O_5$, 557.2078; found, 557.2076.

*(1R,2S,3R,3aR,9bR)-3-Benzoyl-6-methoxy-3′-methyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3ga**).* Following the typical procedure, **3ga** was obtained from **1g** (60.1 mg, 0.2 mmol) and **2a** (57.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL). at 30 °C for 10 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ga** as a white solid (103.5 mg, 93%). Mp: 136.7−137.5 °C. R_f = 0.13 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +219.09 (*c* = 0.25 in CH_2Cl_2). HPLC: 62% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 27.69 min (major), 23.97 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.05 (d, *J* = 8.5 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.35−7.25 (m, 4H), 7.17 (t, *J* = 8.3 Hz, 2H), 7.13−6.98 (m, 4H), 6.90 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 7.5 Hz, 1H), 5.63 (dd, *J* = 10.3, 4.3 Hz, 1H), 4.12 (d, *J* = 10.6 Hz, 1H), 4.04 (d, *J* = 10.3 Hz, 1H), 3.83 (dd, *J* = 10.6, 4.3 Hz, 1H), 3.75 (s, 3H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.4, 172.2, 166.8, 157.2, 147.7, 140.8, 136.8, 135.8, 133.9, 133.7, 129.2, 128.7, 128.42, 128.39, 128.26, 128.0, 125.1, 124.1, 119.1, 118.4, 117.0, 112.3, 72.0, 56.0, 55.9, 52.6, 45.9, 44.0, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2987, 1638, 1483, 1336, 1279, 1152, 689. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{35}H_{29}N_2O_5$, 557.2076; found, 557.2076.

*(1R,2S,3R,3aR,9bR)-3-Benzoyl-6,8-dichloro-3′-methyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3ha**).* Following the typical procedure, **3ha** was obtained from **1h** (68.0 mg, 0.2 mmol) and **2a** (57.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL). at °C for 5 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ha** as a white solid (115.5 mg, 97%). Mp: 213.5−214.3 °C. R_f = 0.25 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +216.50 (*c* = 0.25 in CH_2Cl_2). HPLC: 64% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 12.30 min (major), 13.58 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.00 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.34−7.24 (m, 5H), 7.21 (t, *J* = 7.8 Hz, 2H), 7.16−7.00 (m, 4H), 6.77 (d, *J* = 2.5 Hz, 1H), 5.60 (dd, *J* = 10.2, 4.2 Hz, 1H), 4.09 (d, *J* = 10.9 Hz, 1H), 4.02 (d, *J* = 10.2 Hz, 1H), 3.85 (dd, *J* = 10.9, 4.2 Hz, 1H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm:

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200.8, 172.0, 165.8, 157.1, 146.2, 136.6, 135.6, 133.9, 133.4, 130.5, 129.2, 129.0, 128.8, 128.6, 128.55, 128.50, 128.0, 125.6, 125.5, 123.5, 119.4, 119.2, 72.0, 56.1, 52.4, 45.4, 43.8, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3072, 2914, 1763, 1643, 1499, 1375, 1307, 1146, 749, 689, 663. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{35}Cl^{35}ClN_2O_4$ 595.1188; found, 595.1191. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{35}Cl^{37}ClN_2O_4$, 597.1162; found, 597.1166. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{37}Cl^{37}ClN_2O_4$, 599.1132; found, 599.1156.

(1R,2S,3R,3aR,9bR)-3-(4-Methoxybenzoyl)-3′-methyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione ***(3ia)***. Following the typical procedure, **3ia** was obtained from **1i** (60.1 mg, 0.2 mmol) and **2a** (57.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL). at 30 °C for 8 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ia** as yellow solid (104.5 mg, 91%). Mp: 125.3−126.5 °C. R_f = 0.13 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +299.76 (c = 0.25 in CH_2Cl_2). HPLC: 95% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 41.76 min (major), 49.24 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.09 (d, J = 8.6 Hz, 2H), 7.36−7.26 (m, 4H), 7.22−7.08 (m, 6H), 7.06−6.95 (m, 3H), 6.90 (d, J = 7.8 Hz, 1H), 6.82 (t, J = 8.6 Hz, 2H), 5.57 (dd, J = 10.2, 4.3 Hz, 1H), 4.12 (d, J = 10.6 Hz, 1H), 4.09 (d, J = 10.2 Hz, 1H), 3.79 (s, 3H), 3.78 (dd, J = 10.6, 4.3 Hz, 1H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 199.5, 172.4, 167.5, 164.2, 157.7, 151.2, 136.8, 134.2, 131.8, 129.8, 128.8, 128.7, 128.5, 128.3, 128.0, 127.3, 125.3, 124.3, 119.3, 117.7, 116.2, 113.7, 72.2, 55.9, 55.4, 52.2, 46.0, 44.4, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2876, 1636, 1508, 1454, 1233, 1175, 687. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{35}H_{29}N_2O_5$, 557.2076; found, 557.2076.

(1R,2S,3R,3aR,9bR)-3-(4-Chlorobenzoyl)-3′-methyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione ***(3ja)***. Following the typical procedure, **3ja** was obtained from **1j** (61.2 mg, 0.2 mmol) and **2a** (57.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL). at 30 °C for 5 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ja** as a white solid (105.5 mg, 94%). Mp: 198.1−198.6 °C. R_f = 0.20 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +253.97 (c = 0.25 in CH_2Cl_2). HPLC: 96% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 25.17 min (major), 16.00 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.01 (d, J = 8.5 Hz, 2H), 7.37−7.24 (m, 6H), 7.23−7.08 (m, 6H), 7.07−6.95 (m, 3H), 6.90 (d, J = 7.8 Hz, 1H), 5.57 (dd, J = 10.4, 4.4 Hz, 1H), 4.12 (d, J = 10.9 Hz, 1H), 4.03 (d, J = 10.4 Hz, 1H), 3.82 (dd, J = 10.9, 4.4 Hz, 1H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 200.4, 172.3, 167.5, 157.5, 151.1, 140.4, 136.7, 134.2, 133.8, 130.6, 129.9, 128.9, 128.8, 128.5, 127.9, 127.3, 125.4, 124.4, 119.3, 117.7, 116.0, 72.1, 56.2, 52.7, 45.8, 44.1, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2985, 1638, 1454, 1237, 1211, 1163, 707, 690. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{35}Cl^{35}ClN_2O_4$, 561.1580; found, 561.1581. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{35}Cl^{37}ClN_2O_4$, 563.1552; found, 563.1565.

(1R,2S,3R,3aR,9bR)-3-Benzoyl-3′-isopropyl-1′,2-diphenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione ***(3ab)***. Following the typical procedure, **3ab** was obtained from **1a** (52.9 mg, 0.2 mmol) and **2b** (63.9 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 6 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ab** as a white solid (98.7 mg, 89%). Mp: 103.5−104.3 °C. R_f = 0.25 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +169.36 (c = 0.25 in CH_2Cl_2). HPLC: 71% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 16.55 min (major), 17.57 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.01 (d, J = 8.5 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.24−7.14 (m, 5H), 7.13−7.01 (m, 6H), 6.97 (t, J = 7.5 Hz, 1H), 5.54 (dd, J = 10.2, 4.4 Hz, 1H), 4.25 (d, J = 10.6 Hz, 1H), 4.24 (d, J = 10.2 Hz, 1H), 3.83 (dd, J = 10.6, 4.4 Hz, 1H), 3.13 (septet, J = 6.8 Hz, 1H), 1.61 (d, J = 6.8 Hz, 3H), 1.31 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.6, 172.7, 167.3, 165.0, 151.3, 136.9, 135.9, 135.1, 133.7, 129.8, 129.2, 128.7, 128.50, 128.47, 128.41, 128.3, 128.1, 127.5, 125.3, 124.1, 119.4, 117.7, 116.3, 72.1, 55.4, 54.0, 46.2, 44.4, 27.8, 22.2, 21.9. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3075, 2977, 1637, 1599, 1521, 1152, 692. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{36}H_{31}N_2O_4$, 555.2281; found, 555.2284.

(1R,2S,3R,3aR,9bR)-3-Benzoyl-1′-(4-methoxyphenyl)-3′-methyl-2-phenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione ***(3ac)***. Following the typical procedure, **3ac** was obtained from **1a** (52.9 mg, 0.2 mmol) and **2c** (64.3 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 12 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ac** as an orange solid (101.2 mg, 91%). Mp: 240.5−241.2 °C. R_f = 0.13 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +74.13 (c = 0.25 in CH_2Cl_2). HPLC: 92% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ = 250 nm) t_R = 25.79 min (major), 22.98 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.07 (d, J = 8.3 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.28 (d, J = 7.6 Hz, 2H), 7.21 (t, J = 8.0 Hz, 1H), 7.17−7.07 (m, 5H), 7.04 (d, J = 8.4 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 8.5 Hz, 2H), 5.62 (dd, J = 10.3, 4.3 Hz, 1H), 4.11 (d, J = 10.9 Hz, 1H), 4.05 (d, J = 10.3 Hz, 1H), 3.83 (dd, J = 10.9, 4.3 Hz, 1H), 3.68 (s, 3H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.5, 172.0, 167.4, 157.4, 157.3, 151.2, 135.9, 134.1, 133.7, 129.9, 129.8, 129.2, 128.7, 128.5, 128.3, 128.1, 127.3, 124.2, 121.5, 117.7, 116.3, 113.7, 72.0, 55.9, 55.3, 52.7, 45.8, 44.2, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3147, 2986, 1639, 1512, 1454, 1245, 1167, 742. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{35}H_{29}N_2O_5$, 557.2075; found, 557.2076.

(1R,2S,3R,3aR,9bR)-3-Benzoyl-1′-(4-fluorophenyl)-3′-methyl-2-phenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione ***(3ad)***. Following the typical procedure, **3ad** was obtained from **1a** (52.9 mg, 0.2 mmol) and **2d** (61.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 8 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ad** as an orange solid (96.9 mg, 89%). Mp: 210.9−211.5 °C. R_f = 0.25 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +251.81 (c = 0.25 in CH_2Cl_2). HPLC: 99% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 20.87 min (major), 19.42 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.07 (d, J = 8.4 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.30−7.24 (m, 3H), 7.23−7.18 (m, 1H), 7.17−7.07 (m, 3H), 7.04 (d, J = 8.5 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.4 Hz, 1H), 6.85 (t, J = 8.5 Hz, 2H), 5.62 (dd, J = 10.2, 4.2 Hz, 1H), 4.12 (d, J = 10.8 Hz, 1H), 4.07 (d, J = 10.2 Hz, 1H), 3.82 (dd, J = 10.8, 4.2 Hz, 1H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.3, 172.2, 167.3, 161.2, 158.8, 157.8, 151.1, 135.8, 133.9, 133.8, 132.78, 132.75, 129.9, 129.2, 128.8, 128.5, 128.4, 128.0, 127.3, 124.3, 121.2, 121.1, 117.7, 116.1, 115.4, 115.1, 72.2, 55.9, 52.6, 45.9, 44.2, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3079, 1748, 1637, 1510, 1373, 1283, 1161, 751, 702. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{26}N_2O_4F$, 545.1877; found, 545.1877.

(1R,2S,3R,3aR,9bR)-3-Benzoyl-2-(4-methoxyphenyl)-3′-methyl-1′-phenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione ***(3ae)***. Following the typical procedure, **3ae** was obtained from **1a** (52.9 mg, 0.2 mmol) and **2e** (64.3 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 7 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ae** as a white solid (104.6 mg, 94%). Mp: 244.7−245.5 °C. R_f = 0.10 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +207.35 (c = 0.25 in CH_2Cl_2). HPLC: 90% ee (Chiralpak IA, *n*-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 19.35 min (major), 17.60 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.07 (d, J = 8.4 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 7.40−7.31 (m, 4H), 7.23−7.15 (m, 5H), 7.07−7.01 (m, 2H), 6.98 (td, J = 7.5, 1.2 Hz, 1H), 6.90 (dd, J = 7.65 1.2 Hz, 1H), 6.63 (d, J = 8.5 Hz, 2H), 5.58 (dd, J = 10.4,

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4.3 Hz, 1H), 4.10 (d, J = 10.9 Hz, 1H), 4.01 (d, J = 10.4 Hz, 1H), 3.81 (dd, J = 10.9, 4.3 Hz, 1H), 3.61 (s, 3H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.7, 172.4, 167.5, 159.4, 157.7, 151.2, 136.8, 136.0, 133.7, 129.8, 129.3, 129.2, 128.51, 128.50, 127.3, 125.8, 125.3, 124.3, 119.3, 117.7, 116.2, 114.1, 72.3, 55.6, 55.0, 52.9, 45.8, 44.2, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3027, 2857, 1637, 1516, 1399, 1172, 682. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{35}H_{29}N_2O_5$, 557.2076; found, 557.2076.

(1R,2S,3R,3aR,9bR)-3-Benzoyl-2-(4-bromophenyl)-3′-methyl-1′-phenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3af**). Following the typical procedure, **3af** was obtained from **1a** (52.9 mg, 0.2 mmol) and **2f** (52.9 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 4 d. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3af** as a white solid (117.2 mg, 97%). Mp: 229.3−229.7 °C. R_f = 0.10 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +229.65 (c = 0.25 in CH_2Cl_2). HPLC: 90% ee (Chiralpak IA, n-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 19.76 min (major), 17.20 min (minor). ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.09 (d, J = 7.8 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.43−7.29 (m, 4H), 7.25 (d, J = 6.3 Hz, 1H), 7.22−7.10 (m, 5H), 7.10−7.00 (m, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 5.57 (dd, J = 10.2, 4.2 Hz, 1H), 4.10 (d, J = 10.8 Hz, 1H), 4.08 (d, J = 10.2 Hz, 1H), 3.78 (dd, J = 10.8, 4.2 Hz, 1H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.0, 172.1, 167.2, 157.4, 151.0, 136.6, 135.7, 133.9, 133.2, 131.9, 129.9, 129.7, 129.2, 128.6, 128.5, 127.3, 125.5, 124.3, 122.4, 119.2, 117.7, 115.9, 71.9, 54.9, 52.6, 45.9, 44.2, 13.7. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3092, 2932, 1638, 1494, 1285, 751, 689. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{79}BrN_2O_4$, 605.1076; found, 605.1076. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{26}{}^{81}BrN_2O_4$, 607.1055; found, 607.1061.

(1S,2R,3R,3aR,9bR)-3-Benzoyl-2-(furan-2-yl)-3′-methyl-1′-phenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3ag**). Following the typical procedure, **3ag** was obtained from **1a** (52.9 mg, 0.2 mmol) and **2g** (55.5 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 6 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ag** as a white solid (98.1 mg, 95%). Mp: 248.7−249.3 °C. R_f = 0.20 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +196.45 (c = 0.25 in CH_2Cl_2). HPLC: 86% ee (Chiralpak AD-H, n-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 13.51 min (major), 11.02 min (minor). ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.20 (d, J = 8.3 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.50−7.38 (m, 4H), 7.24−7.17 (m, 3H), 7.12−6.97 (m, 4H), 6.92 (d, J = 7.6 Hz, 1H), 6.21−5.90 (m, 2H), 5.59 (dd, J = 10.2, 4.3 Hz, 1H), 4.22 (d, J = 10.2 Hz, 1H), 4.08 (d, J = 10.6 Hz, 1H), 3.77 (dd, J = 10.6, 4.3 Hz, 1H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.1, 171.9, 167.1, 157.5, 151.0, 148.5, 142.5, 136.9, 135.9, 134.0, 130.0, 129.3, 128.7, 128.6, 127.3, 125.3, 124.3, 119.2, 117.7, 115.8, 110.4, 107.8, 70.1, 51.1, 48.6, 45.6, 43.8, 13.5. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3152, 2917, 1638, 1507, 1459, 1305, 1279, 1075, 700. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{32}H_{25}N_2O_5$, 517.1763; found, 517.1763.

(1S,2R,3R,3aR,9bR)-3-Benzoyl-3′-methyl-1′-phenyl-2-(thiophen-2-yl)-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3ah**). Following the typical procedure, **3ah** was obtained from **1a** (52.9 mg, 0.2 mmol) and **2h** (59.0 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 10 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ah** as a white solid (91.6 mg, 86%). Mp: 238.5−239.2 °C. R_f = 0.20 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +256.82 (c = 0.25 in CH_2Cl_2). HPLC: 92% ee (Chiralpak AD-H, n-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 33.92 min (major), 22.76 min (minor). ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.17 (dd, J = 8.5 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.48−7.34 (m, 4H), 7.24−7.15 (m, 3H), 7.15−6.94 (m, 4H), 6.94−6.88 (m, 2H), 6.72 (dd, J = 5.1, 3.8 Hz, 1H), 5.60 (dd, J = 10.2, 4.4 Hz, 1H), 4.37 (d, J = 10.2 Hz, 1H), 4.09 (d, J = 10.6 Hz, 1H), 3.76 (dd, J = 10.6, 4.4 Hz, 1H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.4, 172.1, 167.1, 157.4, 151.0, 136.9, 136.4, 136.0, 134.0, 130.0, 129.3, 128.59, 128.58, 127.3, 127.1, 126.2, 125.4, 125.3, 124.4, 119.2, 117.8, 115.9, 71.8, 54.0, 50.7, 45.7, 44.0, 13.6. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3079, 2919, 1639, 1498, 1307, 1277, 1031, 746. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{32}H_{25}SN_2O_4$, 533.1535; found, 533.1534.

(1R,2S,3R,3aR,9bR)-3-Benzoyl-3′-methyl-2-(naphthalen-2-yl)-1′-phenyl-2,3,3a,9b-tetrahydro-4H-spiro[cyclopenta[c]chromene-1,4′-pyrazole]-4,5′(1′H)-dione (**3ai**). Following the typical procedure, **3ai** was obtained from **1a** (52.9 mg, 0.2 mmol) and **2i** (68.7 mg, 1.1 equiv) using catalyst **III** (24.3 mg, 0.2 equiv) and benzoic acid (4.99 mg, 0.2 equiv) in toluene (1.0 mL) at 30 °C for 4 days. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) furnished **3ai** as an orange solid (110.6 mg, 96%). Mp: 250.7−251.6 °C. R_f = 0.18 (hexanes/EtOAc = 4:1). $[\alpha]_D^{25}$ = +324.10 (c = 0.25 in CH_2Cl_2). HPLC: 87% ee (Chiralpak IA, n-hexane/EtOH = 85:15, flow rate = 1.0 mL/min, λ= 250 nm) t_R = 19.35 min (major), 17.60 min (minor). ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.09 (d, J = 8.5 Hz, 2H), 7.71−7.57 (m, 4H), 7.51 (dd, J = 8.6, 1.2 Hz, 1H), 7.44−7.34 (m, 3H), 7.34−7.26 (m, 4H), 7.22 (td, J = 7.5, 1.2 Hz, 1H), 7.14 (t, J = 7.6 Hz, 2H), 7.06 (d, J = 8.0 Hz, 1H), 7.04−6.91 (m, 2H), 6.93 (dd, J = 8.0, 1.0 Hz, 1H), 5.75 (dd, J = 10.4, 4.3 Hz, 1H), 4.26 (d, J = 10.4 Hz, 1H), 4.18 (d, J = 10.6 Hz, 1H), 3.86 (dd, J = 10.6, 4.3 Hz, 1H), 2.49 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.7, 172.4, 167.5, 157.6, 151.2, 136.7, 135.9, 133.8, 133.1, 133.0, 131.5, 129.9, 129.3, 128.8, 128.5, 127.8, 127.5, 127.4, 126.25, 126.23, 125.4, 125.1, 124.4, 119.3, 117.8, 116.1, 72.2, 56.3, 52.8, 46.1, 44.4, 13.8. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3227, 3047, 1637, 1499, 1373, 1310, 1165, 751. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{38}H_{29}N_2O_4$, 557.2127; found, 557.2127.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01215.

Copies of the ^1H and ^{13}C NMR spectra of the products, HPLC analysis profiles, X-ray data, and ORTEP diagrams for compounds **3aa** and **3ea** (PDF)

FAIR data, including the primary NMR FID files, for compounds **3aa**−**3ja** and **3ab**−**3ai** (ZIP)

Accession Codes

CCDC 1990595 (**3aa**) and CCDC 1992666 (**3ea**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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