JOC The Journal of Organic Chemistry

Article

Bifunctional Squaramide-Catalyzed Asymmetric [3 + 2] Cyclization of 2-(1-Methyl-2-oxoindolin-3-yl)malononitriles with Unsaturated Pyrazolones to Construct Spirooxindole-Fused Spiropyrazolones

Ye Lin, Bo-Liang Zhao, and Da-Ming Du

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b01268 • Publication Date (Web): 18 Jul 2019

Just Accepted

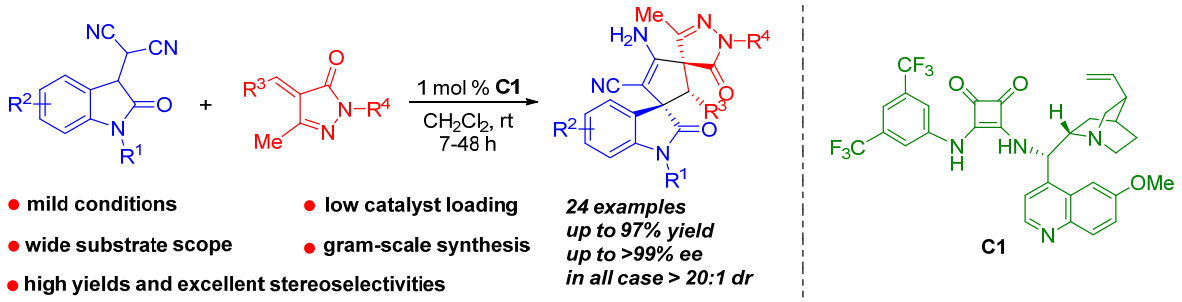
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Bifunctional Squaramide-Catalyzed Asymmetric [3 + 2] Cyclization of 2-(1-Methyl-2-oxoindolin-3-yl)malononitriles with Unsaturated Pyrazolones to Construct Spirooxindole-Fused Spiropyrazolones

Ye Lin, Bo-Liang Zhao, and Da-Ming Du*

School of Chemistry and Chemical Engineering, Beijing Institute of Technology, 5 South Zhongguancun Street, Beijing 100081, People's Republic of China

Fax: (+86)-010-68914985; E-mail: dudm@bit.edu.cn



ABSTRACT: The present paper reports a highly stereoselective synthesis of spirooxindole-fused spiropyrazolones through asymmetric [3 + 2] cyclization reaction of 2-(1-methyl-2-oxoindolin-3-yl)malononitriles with unsaturated pyrazolones under mild conditions. With only 1 mol% of bifunctional squaramide catalyst, a series of chiral dispirocyclic pyrazolone derivatives were attained in high yields (85–97%) with excellent stereoselectivities (up to >99% ee and in all case >20:1 dr). Moreover, gram-scale synthesis and further transformation of the products were also demonstrated.

INTRODUCTION

Over the past decades, spirocyclic compounds have attracted more and more attention from both synthetic and medicinal chemists because of their extensive biological activities.[1] Among the different types of spirocyclic compounds, the highly functionalized spiropyrazolones, spirooxindoles and spiro-oxindole pyrazolones have drawn much attention due to their remarkable and varied biological activities (Figure 1).[2-5] As a consequence, significant efforts have been made to construct these highly valuable spirocyclic

frameworks and a large number of elegant methods have been reported, especially in an asymmetric manner.[6]

However, to the best of our knowledge, the reports on the asymmetric synthesis of the dispirocyclic compounds assembling the oxindole and pyrazolone structures are very limited. For example, in 2013 the Wang's group first reported the organocatalytic [3 + 2] cyclization cascade reaction of unsaturated pyrazolones and isothiocyanato oxindoles to construct spirooxindole-fused spiropyrazolone scaffolds.[7] Since then, several organocatalytic cascade reactions using unsaturated pyrazolones or novel pyrazolone derivatives as synthons for the preparation of spirooxindole-fused spiro-pyrazolones have been successfully developed by the groups of Yuan,[8] Wang,[9] Liu,[10] as well as our group[11] (Scheme 1a–d).

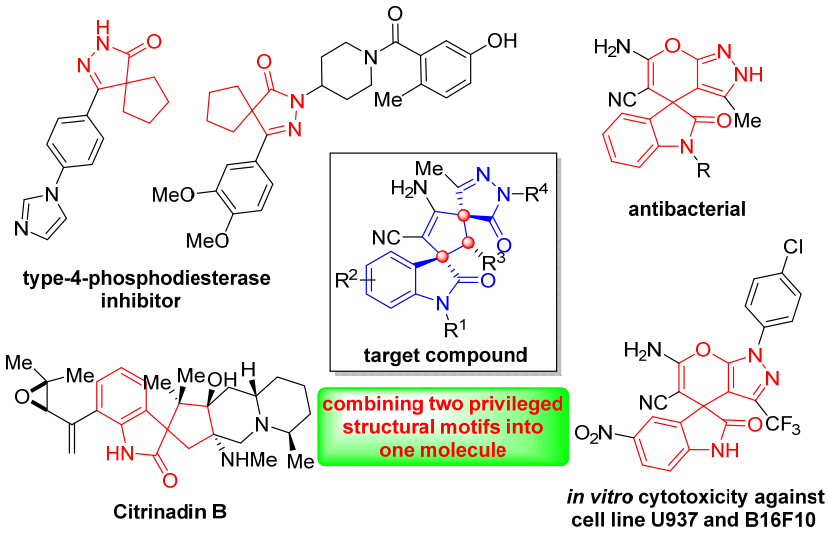
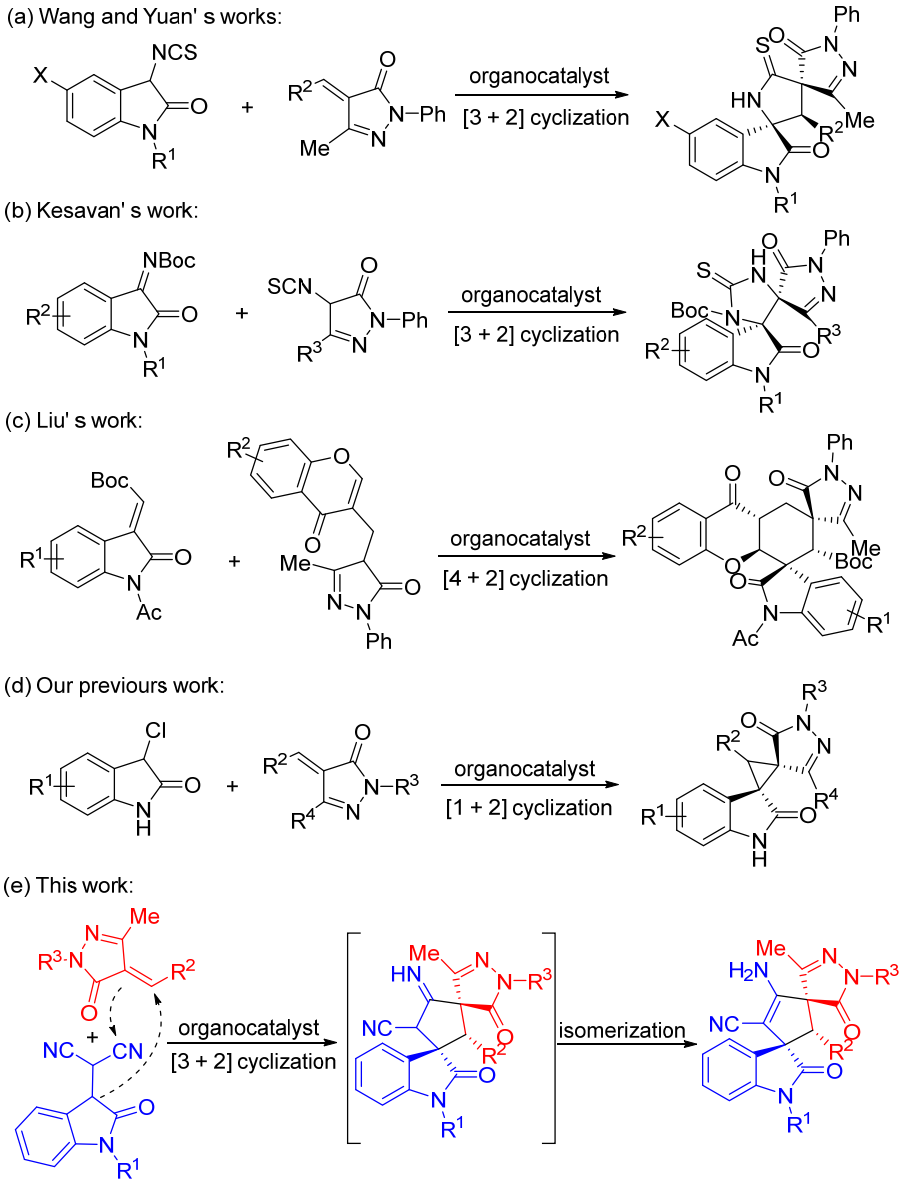


Figure 1. Representative examples of biologically active spiropyrazolones, spirooxindoles and spiro-oxindole pyrazolones.

Indeed, in spite of these efforts devoted to the synthesis of dispirocyclic pyrazolone derivatives, the enantioselective construction of this kind of fused spirocyclic pyrazolones represents still a significant challenge and there is no report on synthesizing sprioxindole-fused spirocyclopentene-pyrazolones bearing multiple contiguous stereocenters. Recently, we noticed that the catalytic cycloadditions of 2-(1-methyl-2-oxoindolin-3-yl)malononitriles used as a kind of highly efficient cascade Michael/cyclization reagent had been reported by Xie.[12] And very recently we have successfuly applied the 2-(1-methyl-2-oxoindolin-3-yl)malononitriles to the asymmetric organocatalytic cascade Michael/cyclization reaction.[13]

Moreover, bifunctional squaramide-catalyzed asymmetric domino/cascade reactions had been well established.[14, 15] In this context, we therefore envisioned that the novel class of spriooxindole-fused spirocyclopentene-pyrazolone derivatives could be obtained via the asymmetric [3 + 2] cyclization reaction of unsaturated pyrazolones and 2-(1-methyl-2-oxoindolin-3-yl)malononitriles (Scheme 1e).

Scheme 1. Previous Strategies on the Asymmetric Construction of Spriooxindole-fused Spiropyrazolone Scaffolds



RESULTS AND DISCUSSION

To test the feasibility, we initially examined the [3 + 2] cyclization reaction with 2-(1-methyl-2-oxoindolin-3-yl)malononitrile **1a** and unsaturated pyrazolone **2a** by using 5 mol % quinine-derived squaramide **C1** in dichloromethane (DCM) at room temperature for 4 h. To our delight, under above conditions, the desired product **3aa** was obtained in 97% yield with >99% ee and >20:1 dr (Table 1, entry 1). With the exciting result in hand, we began to screen some other bifunctional squaramide catalysts **C2**−**C10** (Figure 2) for this [3 + 2] cyclization process (Table 1, entries 2−10). As shown in Table 1, all catalysts could afford the desired product **3aa** in high yields (86−97%) and excellent diastereoselectivity (>20:1 dr), but no improvements were observed. And then, a quinine-derived thiourea **C11** was screen in comparison with squaramides. Although the yield and diastereoselectivity of the reaction maintained, the enantioselectivity declined (Table 1, entry 11). Finally, quinine catalyst **C12** also promoted the reaction, but a significant decline in stereoselectivity (3:1 dr, 26% ee) was obtained. The results indicated that the two hydrogen bonding of the bifunctional catalysts and substituents on the aromatic ring played a pivotal role in controlling the stereoselectivity. Compared with thioureas, squaramides with longer distance between the acidic H atoms could better control the enantioselectivity of this [3 + 2] cyclization reaction.[16] As a result, the squaramide **C1** derived from quinine was proved to be the optimal catalyst for this cascade reaction, considering the yield, diastereoselectivity and enantioselectivity. Subsequently, a rapid solvent screening indicated that acetonitrile and tetrahydrofuran (THF) gave significant decline in diastereoselectivity and reactivity, and the DCM was still the most suitable reaction solvent (Table 1, entries 13−16). Furthermore, by following these promising results, we tested the cascade reaction with a lower catalyst loading of 2.5 mol %. Gratifyingly, the yield and stereoselectivity could be maintained in spite of more reaction time to 8 h (Table 1, entry 17). Moreover, further lowering catalyst loading to 1 mol % led to a set of acceptable results, but a longer reaction time to 12 h was required (Table 1, entry 18). At last, we chose to use the 1 mol % catalyst loading. Thus, the optimum reaction conditions for the [3 + 2] cyclization reaction was the use of 1 mol % catalyst loading of squaramide **C1** in DCM at room temperature.

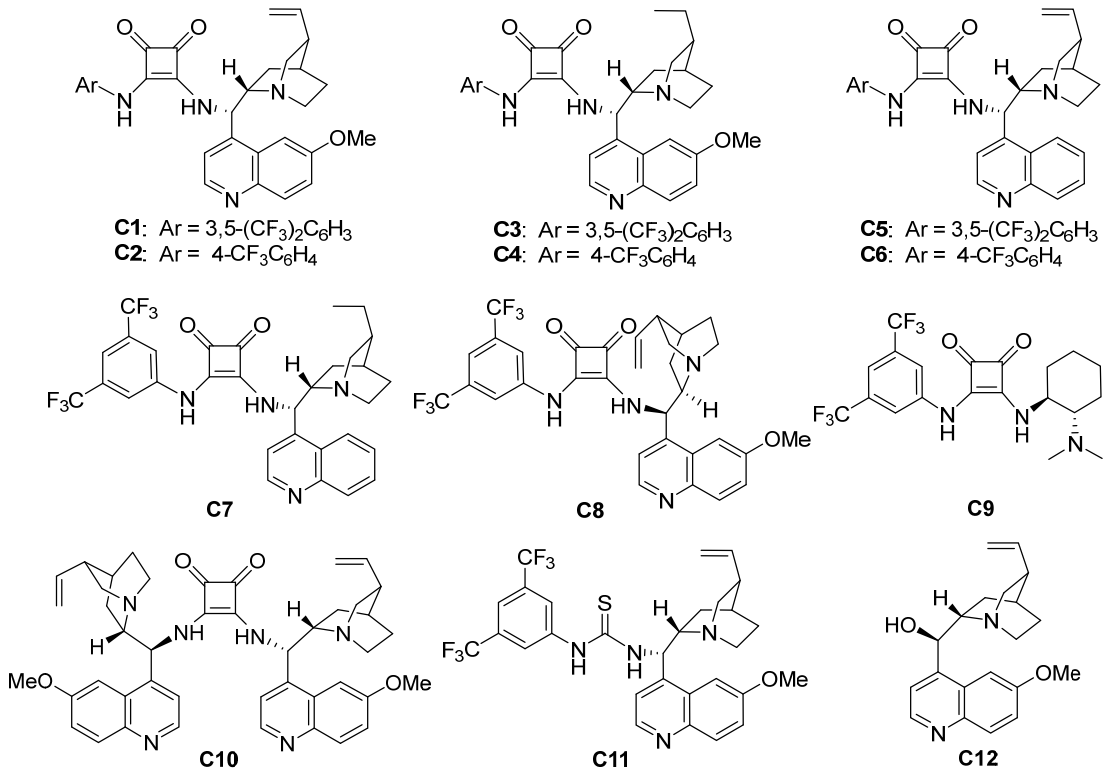
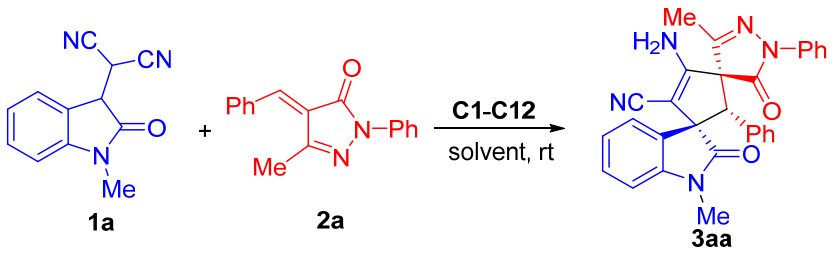


Figure 2. Screened organocatalysts.

With the optimum reaction conditions established, we began to probe the substrate scope of the asymmetric [3 + 2] cyclization for the synthesis of spirooxindole-fused spirocyclopentane-pyrazolones. As summarized in Scheme 2, we firstly examined the tolerance of various 2-(1-methyl-2-oxoindolin-3-yl)-malononitriles **1** under the optimized conditions and the reactions could afford their corresponding products **3ba**−**3ka** in high yields (85−96%) with excellent diastereoselectivities and enantioselectivities (>20:1 dr, 98−>99% ee) in almost all the cases. It was found that regardless of whether the electronic properties or the positions of substituents the reactivity and stereoselectivity were almost unaffected. Only when the *N*-unprotected 2-(1-methyl-2-oxoindolin-3-yl)-malononitrile **1d** was examined, the reactivity was lower and 48 h was needed to complete the reaction but without loss of the yield (96%) and stereoselectivity (>20:1 dr, >99% ee). Moreover, the 7-CF_3 and 5,7-dimethyl substituted oxindole ring of substrates were also well-tolerated under the established conditions to afford the corresponding cycloadducts in good yields and excellent stereoselectivities (Scheme 2, **3ja** and **3ka**).

Table 1. Screening of Organocatalysts and Optimization of the Reaction Conditions [a]



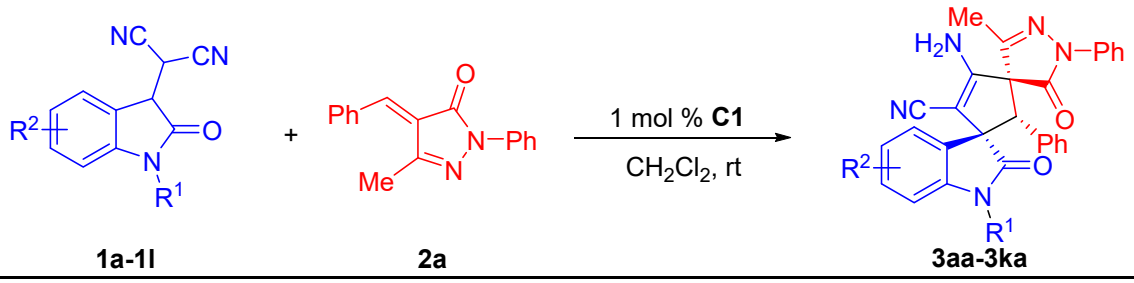
entry	solvent	catalyst	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	CH_2Cl_2	**C1**	4	97	>20:1	>99
2	CH_2Cl_2	**C2**	4	93	>20:1	97
3	CH_2Cl_2	**C3**	4	95	>20:1	>99
4	CH_2Cl_2	**C4**	4	93	>20:1	96
5	CH_2Cl_2	**C5**	4	96	>20:1	>99
6	CH_2Cl_2	**C6**	4	90	>20:1	97
7	CH_2Cl_2	**C7**	4	96	>20:1	>99
8	CH_2Cl_2	**C8**	4	91	>20:1	−94
9	CH_2Cl_2	**C9**	6	86	>20:1	73
10	CH_2Cl_2	**C10**	4	95	>20:1	88
11	CH_2Cl_2	**C11**	6	97	>20:1	86
12	CH_2Cl_2	**C12**	2	95	3:1	−26
13	$CHCl_3$	**C1**	6	95	>20:1	95
14	PhMe	**C1**	5	70	>20:1	97
15	CH_3CN	**C1**	6	81	4:1	>99
16	THF	**C1**	6	85	8:1	>99
17[e]	CH_2Cl_2	**C1**	8	96	>20:1	>99
18[f]	CH_2Cl_2	**C1**	12	96	>20:1	>99

[a]Unless otherwise specified, reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol), and catalyst (5 mol%) in solvent (1.0 mL) at room temperature for 4−12 h. [b]Isolated yield. [c]The dr value was determined by ^{1}H NMR analysis of the crude products. [d]The ee value was determined by HPLC analysis. [e]2.5 mol% catalyst was used. [f]1 mol% catalyst was used.

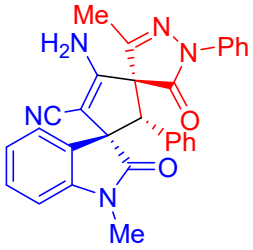
Further exploration of the substrate scope was focused upon structurally diverse unsaturated pyrazolones **2** by reacting to **1a**. As shown in Scheme 3, various aromatic ring substitutions at the R^3 position were tolerated, facilely generating the desired products **3ab**–**3aj** in high yields with excellent stereocontrol (>20:1 dr, >99% ee). Even the R^3 were the heteroaromatic 2-furyl and 2-thienyl substituents, the cascade process was compatible (Scheme 3, **3ak** and **3al**). In addition, when the different electronic nature ofaro-matic ring substitutions were introduced on the R^4 position of the unsaturated pyrazolones, facile con

versions were also observed and the corresponding products (Scheme 3, **3am** and **3an**) were attained in

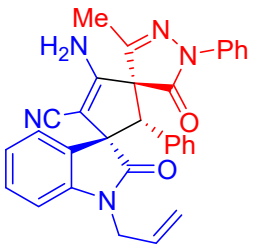
Scheme 2. Substrate Scope of 2-(1-methyl-2-oxoindolin-3-yl)malononitriles[a,b,c,d]



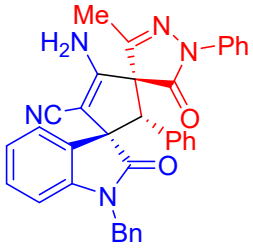
1a-1l **2a** **3aa-3ka**



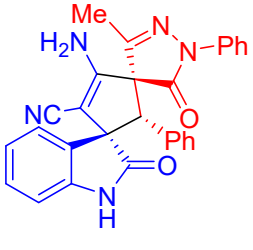
3aa
12 h, 96% yield
>20:1 dr, >99% ee



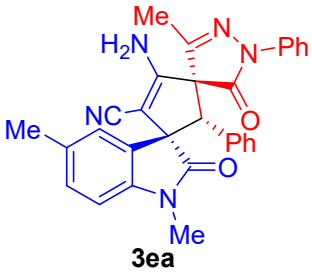
3ba
12 h, 88% yield
>20:1 dr, >99% ee



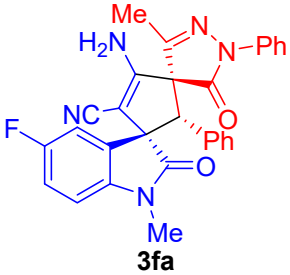
3ca
12 h, 87% yield
>20:1 dr, >99% ee



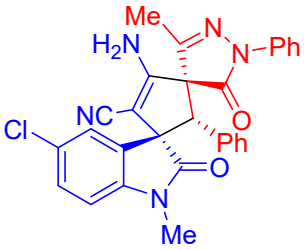
3da
48 h, 96% yield
>20:1 dr, >99% ee



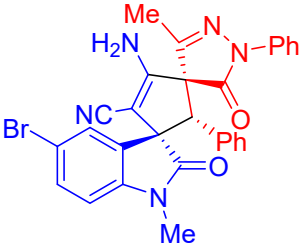
3ea
12 h, 95% yield
>20:1 dr, >99% ee



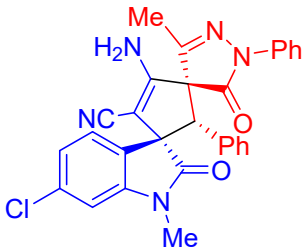
3fa
12 h, 91% yield
>20:1 dr, >99% ee



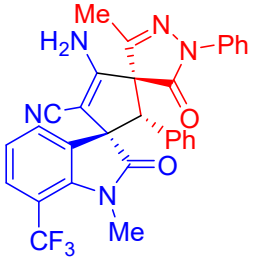
3ga
12 h, 87% yield
>20:1 dr, 99% ee



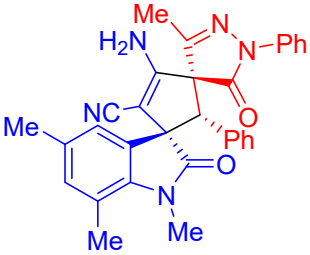
3ha
12 h, 85% yield
>20:1 dr, >99% ee



3ia
12 h, 90% yield
>20:1 dr, >99% ee



3ja
12 h, 89% yield
>20:1 dr, 98% ee

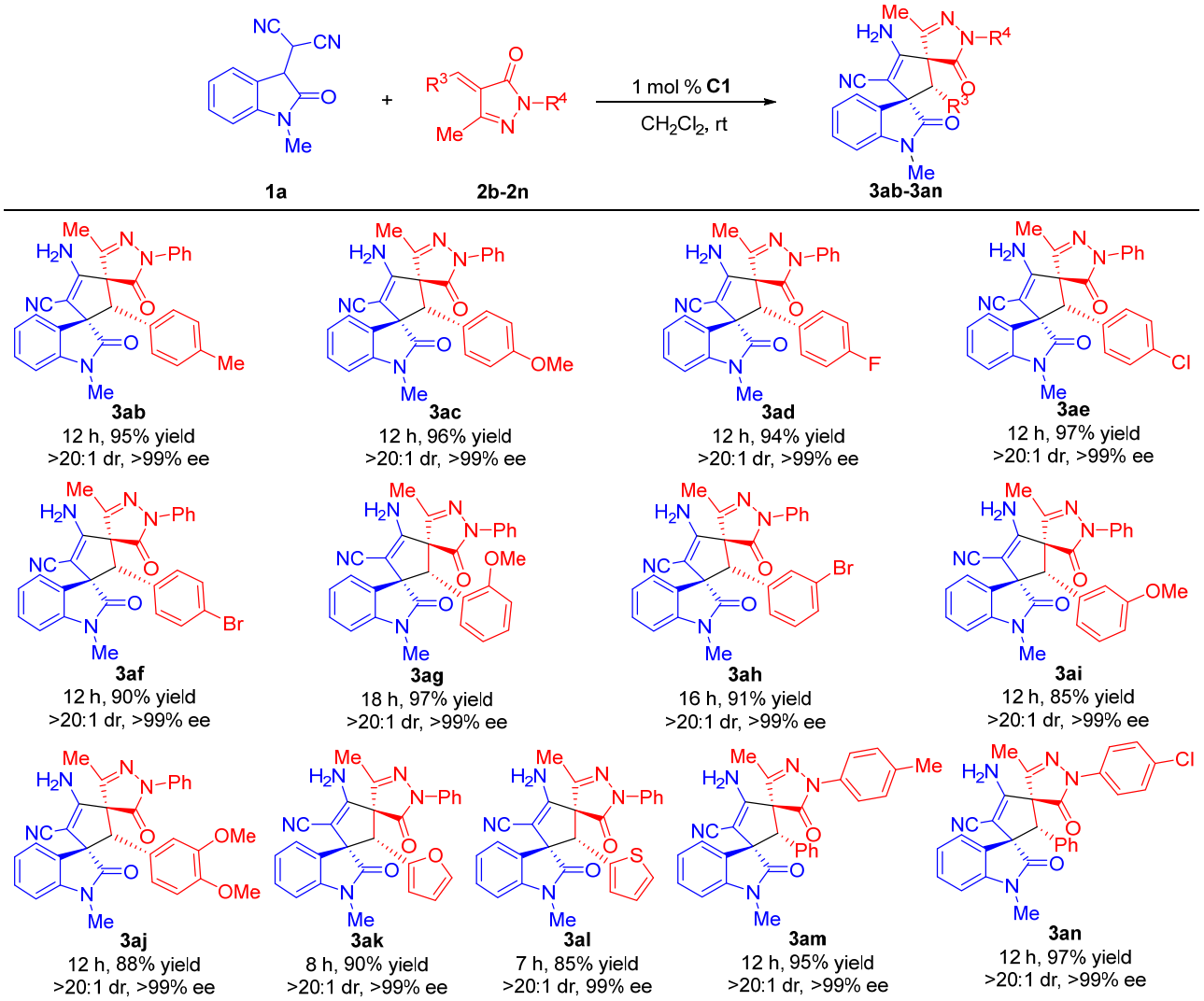


3ka
12 h, 93% yield
>20:1 dr, >99% ee

[a]Unless otherwise specified, reactions were carried out with **1** (0.1 mmol), **2a** (0.12 mmol), and catalyst **C1** (1 mol%) in 1.0 ml CH_2Cl_2 were stirred at room temperature for 12−48 h. [b]Isolated yield. [c]The dr values of products were determined by ^1H NMR analysis of the crude products. [d]The ee value was determined by HPLC.

satisfactory yields (95−97%) with excellent diastereo- and enantioselectivities (>20:1 dr, >99% ee). The absolute configuration of the product **3af** was unambiguously determined by single-crystal X-ray diffraction analysis as (2'*R*,3*R*,3'*S*) (Figure 3).[17] The stereochemistry of the other products was tentatively assigned by analogy

Scheme 3. Substrate Scope of Unsaturated Pyrazolones[a,b,c,d]



[a]Unless otherwise specified, reactions were carried out with **1a** (0.1 mmol), **2** (0.12 mmol), and catalyst **C1** (1 mol%) in 1.0 ml CH_2Cl_2 were stirred at room temperature for 7−18 h. [b]Isolated yield. [c]The dr values of products were determined by ^{1}H NMR analysis of the crude products. [d]The ee value was determined by HPLC.

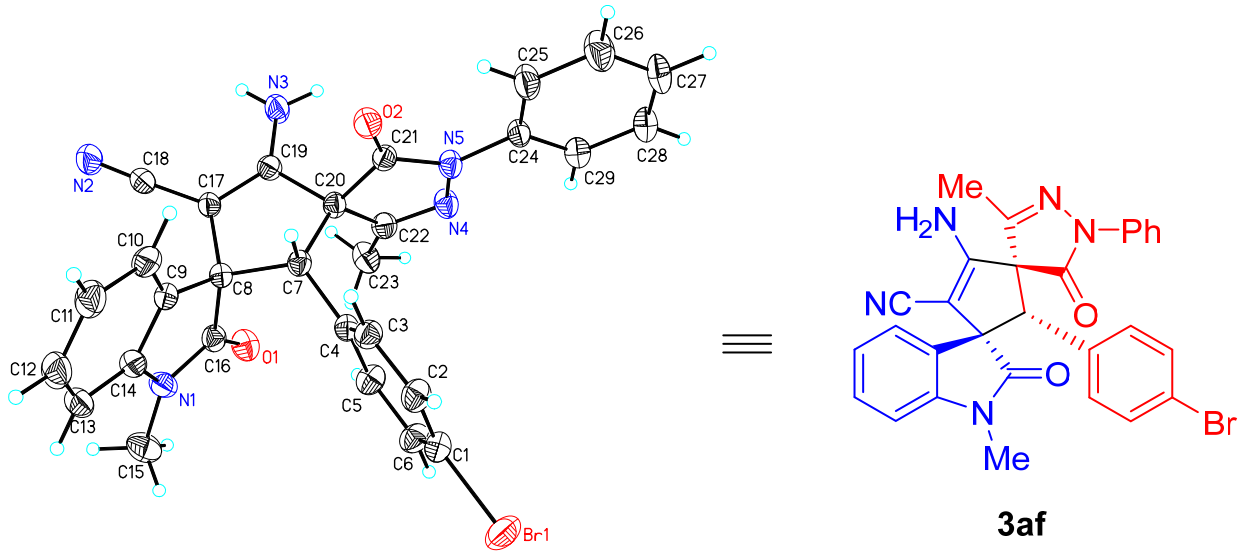
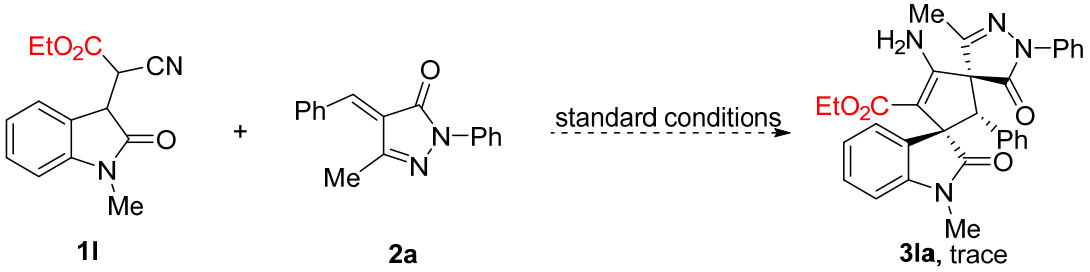


Figure 3. X-ray crystal structure of **3af**. (Displacement ellipsoids are drawn at the 50% probability level, and another symmetric molecule and two included ethyl acetate molecules were omitted for clarity)

Having investigated the cyclization reaction between a wide range of 2-(1-methyl-2-oxoindolin-3-yl)malononitriles with unsaturated pyrazolones, we then turned our attention to ethyl 2-cyano-2-(1-methyl-2-oxoindolin-3-yl)acetates. However, under the standard conditions, only trace reaction between ethyl 2-cyano-2-(1-methyl-2-oxoindolin-3-yl)acetate **1l** and unsaturated pyrazolone **2a** was detected, indicating the relatively lower reactivity of **1l** (Scheme 4).

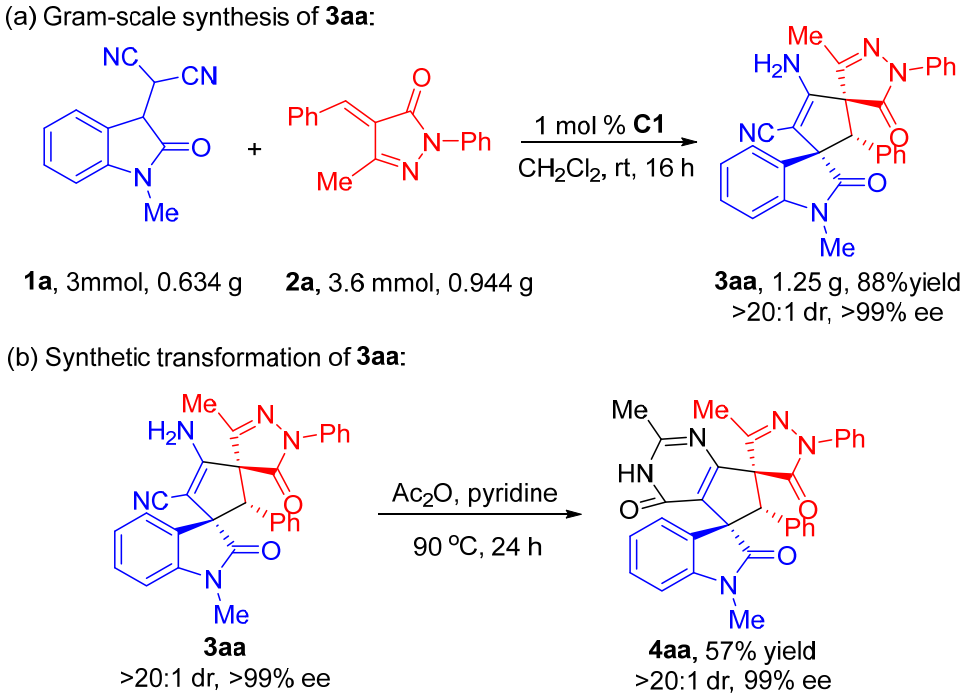
Scheme 4. Evaluation of Ethyl 2-cyano-2-(1-methyl-2-oxoindolin-3-yl)acetate Substrates



To further illustrate the robustness and practicality of this asymmetric cyclization reaction, the gram-scale experiment between **1a** and **2a** was carried out under the optimal reaction conditions (Scheme 5a). Gratifyingly, the dispirocyclic compound **3aa** was obtained in a comparable yield with maintained stereoselectivities. In addition, a further structural conversion was conducted by treatment of optically pure

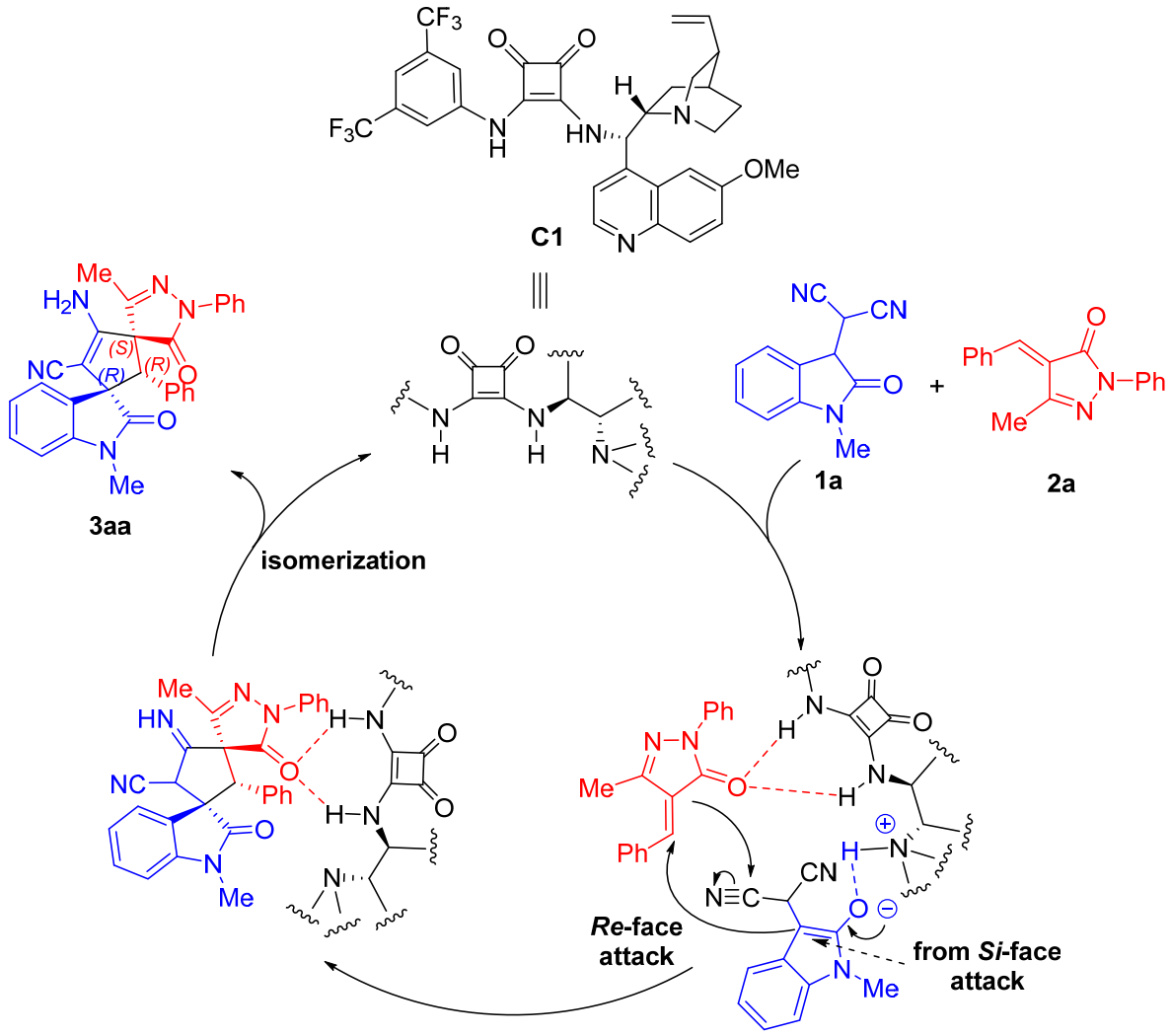
3aa and acetic anhydride with pyridine at 90 °C for 24 h. The corresponding product **4aa** was attained in 57% yield without sacrifice to the diastereo- and enantioselectivity (Scheme 5b).[18]

Scheme 5. Gram-scale Synthesis and Functional Group Transformation of 3aa



Finally, for a better understanding of this [3 + 2] cyclization reaction, we proposed a plausible mechanism on the basis of previous literature report[12] and our experiment results. As shown in Scheme 6, on the one hand, the 2-(1-methyl-2-oxoindolin-3-yl)-malononitrile **1a** was deprotonated by the tertiary amine moiety of catalyst **C1**. On the other hand, unsaturated pyrazolone **2a** was activated by two hydrogen bonding from the amide N−H. Subsequently, the deprotonated activation of 2-(1-methyl-2-oxoindolin-3-yl)-malononitrile **1a** predominantly from the *Si* face attacked the *Re* face of the electron-deficient unsaturated pyrazolone **2a** which underwent the intramolecular Michael addition. Simultaneously, the Michael adduct intermediate followed by intramolecular cyclization/isomerization sequence to afford the desired product **3aa** and regenerate the bifunctional squaramide catalyst **C1**.

Scheme 6. Proposed Mechanism for [3 + 2] Cyclization Reaction



In conclusion, we have developed a highly stereoselective synthesis of spirooxindole-fused spirocyclopentene-pyrazolones through asymmetric [3 + 2] cyclization reaction of 2-(1-methyl-2-oxoindolin-3-yl)-malononitriles with unsaturated pyrazolones under mild conditions. With only 1 mol % of bifunctional squaramide catalyst loading, a series of chiral dispirocyclic pyrazolone derivatives were attained in high yields (85−97%) with excellent stereoselectivities (up to >99% ee and in all case >20:1 dr). In addition, gram-scale synthesis and further transformation of the product 3aa were also demonstrated with excellent stereoselectivities. This elegant strategy provides a novel class of medicinally promising spirooxindole-fused spiropyrazolone skeletons.

EXPERIMENTAL SECTION

General Information.

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was performed with silica gel (200-300 mesh). Melting points were determined with an melting-point apparatus and are uncorrected. ^{1}H NMR spectra were measured with 400 MHz spectrometer in acetone-d6 and $CDCl_3$, chemical shifts were reported in δ (ppm) units relative to tetramethylsilane (TMS) as the internal standard. $^{13}C\{^{1}H\}$ NMR spectra were measured at 176 MHz with 700 MHz spectrometer in acetone-d6 and $CDCl_3$, chemical shifts were reported in ppm relative to TMS with the solvent resonance as internal standard (acetone-d6 at 30.83 ppm, $CDCl_3$ at 77.00 ppm). $^{19}F\{^{1}H\}$ NMR spectra were measured at 377 MHz with 400 MHz spectrometer. Proton coupling patterns are described as broad (br) singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). High resolution mass spectra were measured with an Accurate-Mass-Q-TOF MS system equipped with an electrospray ionization (ESI) source. Enantiomeric excesses were determined by chiral HPLC analysis using an LC instrument with a Chiralpak IB and AD-H column.

Materials.

The arylidene azlactones **2a**–**2n** were prepared according to the reported literature procedures.[19]

Synthesis of 2-(1-methyl-2-oxoindolin-3-yl)-malononitriles 1a–1l.

In a 50 ml flame-dried flask was added isatin (3.0 mmol) in anhydrous EtOH (10 mL), and then malononitrile or ethyl 2-cyanoacetate (3.2 mmol) was added. After that, the mixture was heated 2 h at reflux. Then, the precipitated solid was collected by filtration and recrystallized from ethanol affording the malonylisatinylidene derivatives or ethyl 2-cyano-2-(1-methyl-2-oxoindolin-3-ylidene)acetates.

Next, the malonylisatinylidene derivatives (1.00 mmol) and Hantzsch ester (1.05 mmol) were combined in EtOH (15 mL) and left stirring at room temperature for 15–30 min. After the reaction was finished, the

reaction mixture was isolated by evaporating the solvent, taking up the residue in ethyl acetate, and extracting with aqueous HCl (1.0 mol/L). The crude product after drying over Na_2SO_4, filtration, and evaporation of the solvent was filtered through a short column of silica eluting with petroleum ether/ethyl acetate (2/1 to 1/1 v/v) to give the desired products **1a**–**1l** in the range of 60–80 % yields.

Reported compounds 2-(1-methyl-2-oxoindolin-3-yl)-malononitriles **1a**, **1d** were prepared according to the literature.[20] The new substrates **1b**, **1c** and **1e**–**1l** were obtained according to the literature procedure with functional group modifications, and the detailed data was listed below.[20]

2-(1-Methyl-2-oxoindolin-3-yl)malononitrile (1a).[20] White solid, 147.8 mg, 70% yield, mp 131–133 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.51 (d, J = 7.6 Hz, 1H), 7.43 (tt, J_1 = 7.8 Hz, J_2 = 0.8 Hz, 1H), 7.16 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 5.69 (d, J = 8.4 Hz, 1H), 4.53 (d, J = 4.8 Hz, 1H), 3.18 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, DMSO-d6): δ 171.8, 144.4, 129.8, 124.2, 122.7, 112.5, 112.2, 109.2, 43.4, 26.2, 23.8 ppm.

2-(1-Allyl-2-oxoindolin-3-yl)malononitrile (1b). White solid, 185.0 mg, 78% yield, mp 108–110 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.53 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.16 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 5.88–5.78 (m, 1H), 5.73 (d, J = 4.4 Hz, 1H), 5.22–5.15 (m, 2H), 4.60 (d, J = 4.4 Hz, 1H), 4.45–4.39 (m, 1H), 4.34–4.27 (m, 1H) ppm. ^{13}C{^{1}H} NMR (176 MHz, DMSO-d6): δ 171.6, 143.4, 131.1, 129.7, 124.3, 122.8, 116.8, 112.6, 112.2, 109.8, 43.5, 41.6, 23.8 ppm.

2-(1-Benzyl-2-oxoindolin-3-yl)malononitrile (1c). White solid, 229.9 mg, 80% yield, mp 114–116 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.55 (d, J = 7.6 Hz, 1H), 7.38–7.25 (m, 6H), 7.14 (td, J_1 = 7.6 Hz, J_2 = 0.4 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 5.80 (d, J = 8.8 Hz, 1H), 5.04 (d, J = 16.0 Hz, 1H), 4.90 (d, J = 15.6 Hz, 1H), 4.70 (d, J = 4.4 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (176 MHz, DMSO-d6): δ 172.1, 143.3, 135.6, 129.7, 128.5, 127.4, 127.1, 124.4, 122.9, 122.8, 112.6, 112.3, 109.8, 43.5, 42.9, 23.8 ppm.

2-(2-Oxoindolin-3-yl)malononitrile (1d).[20] White solid, 122.3 mg, 62% yield, mp 161–163 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ 10.90 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.33 (tt, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1H),

7.08 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 5.64 (d, J = 4.4 Hz, 1H), 4.44 (d, J = 4.4 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d6): δ 173.6, 143.0, 129.7, 124.4, 123.6, 122.1, 112.6, 112.3, 110.1, 43.9, 23.7 ppm.

2-(1,5-Dimethyl-2-oxoindolin-3-yl)malononitrile (1e). White solid, 153.2 mg, 68% yield, mp 125–127 °C. ^1H NMR (400 MHz, DMSO-d6): δ 7.32 (s, 1H), 7.24 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 5.65 (d, J = 4.0 Hz, 1H), 4.47 (d, J = 4.4 Hz, 1H), 3.16 (s, 3H), 2.32 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d6): δ 171.6, 142.0, 131.8, 130.0, 124.8, 122.8, 112.6, 112.2, 108.9, 43.5, 26.2, 23.8, 20.6 ppm.

2-(5-Fluoro-1-methyl-2-oxoindolin-3-yl)malononitrile (1f). White solid, 144.4 mg, 63% yield, mp 131–133 °C. ^1H NMR (400 MHz, DMSO-d6): δ 7.39–7.36 (m, 1H), 7.32–7.27 (m, 1H), 7.14 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1H), 5.72 (d, J = 4.4 Hz, 1H), 4.57 (d, J = 4.4 Hz, 1H), 3.18 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d6): δ 171.7, 158.3 (d, J = 238.1 Hz), 140.7, 124.4 (d, J = 9.0 Hz), 116.1 (d, J = 23.4 Hz), 112.3 (d, J = 25.9 Hz), 112.2, 112.1, 110.2 (d, J = 8.1 Hz), 43.7, 26.4, 23.6 ppm.

2-(5-Chloro-1-methyl-2-oxoindolin-3-yl)malononitrile (1g). White solid, 169.5 mg, 69% yield, mp 156–158 °C. ^1H NMR (400 MHz, DMSO-d6): δ 7.55–7.54 (m, 1H), 7.52–7.49 (m, 1H), 7.16 (d, J = 4.4 Hz, 1H), 5.73 (d, J = 4.4 Hz, 1H), 4.57 (d, J = 4.4 Hz, 1H), 3.18 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d6): δ 171.6, 143.3, 129.6, 126.6, 124.7, 124.5, 112.2, 112.1, 110.7, 43.5, 26.4, 23.6 ppm.

2-(5-bromo-1-methyl-2-oxoindolin-3-yl)malononitrile (1h). White solid, 174.1 mg, 60% yield, mp 165–167 °C. ^1H NMR (400 MHz, DMSO-d6): δ 7.67–7.66 (m, 1H), 7.65–7.62 (m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 5.73 (d, J = 4.4 Hz, 1H), 4.58 (d, J = 4.4 Hz, 1H), 3.18 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d6): δ 171.5, 143.8, 132.5, 127.2, 125.1, 114.2, 112.2, 112.1, 111.2, 43.4, 26.4, 23.5 ppm.

2-(6-Chloro-1-methyl-2-oxoindolin-3-yl)malononitrile (1i). White solid, 174.5 mg, 71% yield, mp 134–136 °C. ^1H NMR (400 MHz, DMSO-d6): δ 7.49 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.23 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 5.69 (d, J = 4.4 Hz, 1H), 4.54 (d, J = 4.4 Hz, 1H), 3.18

(s, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (176 MHz, DMSO-d6): δ 171.9, 145.9, 134.4, 125.6, 122.3, 121.6, 112.3, 112.1, 109.8, 43.1, 26.5, 23.7 ppm.

2-(1-Methyl-2-oxo-7-(trifluoromethyl)indolin-3-yl)malononitrile (1j). White solid, 215.0 mg, 77% yield, mp 101–103 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.82 (d, J = 7.2 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 5.76 (d, J = 4.8 Hz, 1H), 4.66 (d, J = 4.4 Hz, 1H), 3.33 (q, J = 2.4 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (176 MHz, DMSO-d6): δ 173.1, 142.0, 128.6, 127.3 (q, J = 5.6 Hz), 125.7, 123.3 (q, J = 271.4 Hz), 122.7, 112.12, 112.06, 111.3 (q, J = 32.6 Hz), 42.2, 28.7 (q, J = 6.0 Hz), 23.9 ppm.

2-(1,5,7-Trimethyl-2-oxoindolin-3-yl)malononitrile (1k). Brownish yellow solid, 177.1 mg, 74% yield, mp 136–138 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.15 (s, 1H), 6.98 (s, 1H), 5.62 (d, J = 4.4 Hz, 1H), 4.41 (d, J = 4.4 Hz, 1H), 3.42 (s, 3H), 2.51 (s, 3H), 2.26 (s, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (176 MHz, DMSO-d6): δ 172.2, 139.6, 133.6, 131.6, 123.3, 122.5, 120.1, 112.6, 112.3, 43.2, 29.2, 24.0, 20.3, 18.1 ppm.

Ethyl 2-cyano-2-(1-methyl-2-oxoindolin-3-yl)acetate (1l). (Diastereoisomeric mixture, ratio 1.2 : 1.) White solid, 162.7 mg, 63% yield, mp 111–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 and 7.23 (d, J = 7.6 Hz, 2 × 1H), 7.38–7.33 (m, 2 × 1H), 7.082 and 7.078 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 2 × 1H), 6.90 and 6.87 (d, J = 8.0 Hz, 2 × 1H), 4.43 and 4.35 (d, J = 3.2 Hz, 2 × 1H), 4.39 (q, J = 7.2 Hz, 2 × 1H), 4.11 and 3.94 (d, J = 3.2 Hz, 2 × 1H), 4.10–4.01 (m, 2 × 1H), 3.23 and 3.22 (s, 2 × 3H), 1.37 and 1.06 (t, J = 7.2 Hz, 2 × 3H) ppm. $^{13}C\{^{1}H\}$ NMR (176 MHz, $CDCl_3$): δ 172.93, 172.91; 164.4, 163.0; 144.5, 144.3; 129.5, 129.3; 124.2, 123.6; 123.5, 123.3; 122.9, 122.7; 115.2, 113.3; 108.6, 108.3; 63.4, 62.8; 44.52, 44.46; 38.7, 37.6; 26.32, 26.26; 13.7, 13.4 ppm.

General Procedure for the asymmetric [3 + 2] cyclization reaction.

2-(1-Methyl-2-oxoindolin-3-yl)malononitriles **1** (0.10 mmol), unsaturated pyrazolinones **2** (0.12 mmol), and catalyst **C1** (0.6 mg, 0.001 mmol) were dissolved in CH_2Cl_2 (0.5 mL), and the mixture was stirred at room temperature for 12–48 h. After completion of the reaction, the reaction mixture was concentrated

and directly purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4/1 to 2/1 v/v) to afford the pure products **3** as solid**.**

(2'*R*,3*R*,3'*S*)-4'-Amino-1,3''-dimethyl-2,5''-dioxo-1'',2'-diphenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3aa). From 21.1 mg (0.10 mmol) **1a** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3aa** as a white solid (45.5 mg, 96%), mp 216–218 °C. HPLC (Daicel Chiralpak AD-H, n-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 17.1 min (minor), t_R = 18.9 min (major); >99% ee. $[\alpha]_D^{20}$ = –131.0 (*c* = 2.00, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.83–7.81 (m, 2H), 7.54 (dd, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H), 7.39–7.34 (m, 2H), 7.32 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.21 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.18–7.14 (m, 1H), 7.13–7.07 (m, 3H), 7.02–7.00 (m, 2H), 6.88 (d, J = 7.6 Hz, 1H), 6.70 (br s, 2H), 4.53 (s, 1H), 3.09 (s, 3H), 2.71 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 178.0, 173.9, 161.6, 160.8, 145.4, 139.9, 134.4, 132.3, 131.3, 130.5, 130.34, 130.33, 130.27, 126.8, 125.1, 125.0, 120.3, 116.8, 110.3, 82.8, 73.4, 66.1, 64.5, 27.6, 18.1 ppm. HRMS (ESI-TOF): m/z calcd. for $C_{29}H_{24}N_5O_2$ $[M + H]^+$ 474.1925, found 474.1923.

(2'*R*,3*R*,3'*S*)-1-Allyl-4'-amino-3''-methyl-2,5''-dioxo-1'',2'-diphenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ba). From 23.7 mg (0.10 mmol) **1b** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ba** as a light yellow solid (43.9 mg, 88% yield), mp 131–133 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 12.7 min (minor), t_R = 17.0 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –107.9 (*c* = 2.14, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.83–7.80 (m, 2H), 7.57 (dd, J_1 = 7.2 Hz, J_2 = 1.0 Hz, 1H), 7.39–7.34 (m, 2H), 7.29 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.22 (td, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 1H), 7.18–7.08 (m, 4H), 7.04–7.01 (m, 2H), 6.82 (d, J = 7.2 Hz, 1H), 6.73 (br s, 2H),

5.64–5.55 (m, 1H), 4.94 (dd, J_1 = 10.4 Hz, J_2 = 1.2 Hz, 1H), 4.74 (dd, J_1 = 17.2 Hz, J_2 = 1.2 Hz, 1H), 4.55 (s, 1H), 4.43–4.36 (m, 1H), 4.22–4.16 (m, 1H), 2.75 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, acetone-d6): δ 177.7, 173.9, 161.6, 160.8, 144.6, 139.9, 134.2, 132.8, 132.2, 131.2, 130.7, 130.5, 130.4, 130.3, 126.8, 125.14, 125.10, 120.2, 117.9, 116.9, 111.1, 82.8, 73.4, 66.4, 64.7, 43.6, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{31}H_{26}N_5O_2$ $[M + H]^+$ 500.2081, found 500.2084.

(2'*R*,3*R*,3'*S*)-4'-Amino-1-benzyl-3''-methyl-2,5''-dioxo-1'',2'-diphenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ca). From 28.7 mg (0.10 mmol) **1c** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ca** as a white solid (47.6 mg, 87% yield), mp 201–203 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 15.3 min (minor), t_R = 25.7 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –74.7 (*c* = 1.91, acetone). ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.6 Hz, 2H), 7.58–7.56 (m, 1H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.22–7.11 (m, 7H), 7.05 (t, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 7.6 Hz, 2H), 6.76 (d, *J* = 6.8 Hz, 2H), 6.54–6.52 (m, 1H), 5.07 (d, *J* = 16.0 Hz, 1H), 4.84 (br s, 2H), 4.62 (s, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 2.74 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 175.8, 171.5, 160.6, 157.9, 142.3, 137.2, 134.7, 131.9, 129.6, 129.5, 129.0, 128.8, 128.6, 128.55, 128.46, 127.3, 126.6, 125.7, 123.8, 123.7, 118.9, 114.7, 109.4, 83.9, 71.4, 63.3, 62.8, 44.0, 17.0 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{35}H_{28}N_5O_2$ $[M + H]^+$ 550.2238, found 550.2227.

(2'*R*,3*R*,3'*S*)-4'-Amino-3''-methyl-2,5''-dioxo-1'',2'-diphenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3da). From 19.7 mg (0.10 mmol) **1d** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (3/1 to 2/1 v/v) as eluent to obtain **3da** as a light pink solid (44.1 mg, 96% yield), mp 146–148 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 24.1 min (minor), t_R = 29.0 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –117.9 (*c*

= 1.68, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 9.55 (s, 1H), 7.84–7.81 (m, 2H), 7.52 (d, J = 7.2 Hz, 1H), 7.39–7.35 (m, 2H), 7.24 (td, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 1H), 7.19–7.09 (m, 7H), 6.83 (d, J = 7.2 Hz, 1H), 6.68 (br s, 2H), 4.54 (s, 1H), 2.69 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 179.6, 174.0, 161.6, 160.6, 143.6, 139.9, 134.6, 133.0, 131.2, 130.5, 130.4, 130.2, 126.8, 125.4, 124.6, 120.3, 116.9, 111.6, 83.3, 73.5, 66.0, 64.9, 18.0 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{28}H_{22}N_5O_2$ $[M + H]^+$ 460.1768, found 460.1767.

(2'*R*,3*R*,3'*S*)-4'-Amino-1,3'',5-trimethyl-2,5''-dioxo-1'',2'-diphenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ea). From 22.5 mg (0.10 mmol) **1e** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ea** as a white solid (46.4 mg, 95% yield), mp 96–98 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 11.1 min (minor), t_R = 12.8 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –65.9 (*c* = 2.04, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.83 (d, J = 7.6 Hz, 2H), 7.39–7.35 (m, 3H), 7.17 (t, J = 7.6 Hz, 1H), 7.13–7.07 (m, 4H), 7.03–7.02 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 6.68 (br s, 2H), 4.52 (s, 1H), 3.07 (s, 3H), 2.70 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 177.9, 174.0, 161.7, 160.6, 143.1, 139.9, 134.6, 134.5, 132.3, 131.6, 130.5, 130.3, 130.2, 126.8, 125.6, 120.3, 116.9, 110.1, 83.0, 73.5, 66.0, 64.6, 55.9, 27.6, 22.1, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{30}H_{26}N_5O_2$ $[M + H]^+$ 488.2081, found 488.2078.

(2'*R*,3*R*,3'*S*)-4'-Amino-5-fluoro-1,3''-dimethyl-2,5''-dioxo-1'',2'-diphenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3fa). From 22.9 mg (0.10 mmol) **1f** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3fa** as a brownish yellow solid (44.7 mg, 91% yield), mp 117–119 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 13.1 min (minor), t_R = 16.3 min

(major); >99% *ee*. $[\alpha]_D^{20}$ = –110.6 (*c* = 2.04, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.39–7.32 (m, 3H), 7.19–7.09 (m, 5H), 7.06–7.03 (m, 2H), 6.91 (dd, J_1 = 8.4 Hz, J_2 = 4.0 Hz, 1H), 6.80 (br s, 2H), 4.47 (s, 1H), 3.10 (s, 3H), 2.71 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 177.8, 173.8, 161.44 (d, *J* = 239.5 Hz), 161.39, 161.1, 151.6, 141.6, 139.9, 134.2 (d, *J* = 7.2 Hz), 134.1, 130.5, 130.4, 126.9, 125.5, 120.3, 117.6 (d, *J* = 23.6 Hz), 116.7, 112.9 (d, *J* = 25.5 Hz), 111.4 (d, *J* = 8.4 Hz), 82.1, 73.4, 66.2, 65.0, 27.7, 18.1 ppm. ^{19}F{^{1}H} NMR (377 MHz, acetone-d6): δ –115.9 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{29}H_{23}FN_5O_2$ $[M + H]^+$ 492.1830, found 492.1817.

(2'*R*,3*R*,3'*S*)-4'-Amino-5-chloro-1,3''-dimethyl-2,5''-dioxo-1'',2'-diphenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ga). From 24.6 mg (0.10 mmol) **1g** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ga** as a white solid (44.2 mg, 87% yield), mp 100–102 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 12.4 min (minor), t_R = 14.8 min (major); 99% *ee*. $[\alpha]_D^{20}$ = –14.5 (*c* = 1.81, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.83–7.80 (m, 2H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.40–7.35 (m, 3H), 7.19–7.11 (m, 4H), 7.05–7.03 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.81 (br s, 2H), 4.47 (s, 1H), 3.11 (s, 3H), 2.70 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 177.7, 173.7, 161.3, 161.1, 144.3, 139.8, 134.4, 134.0, 131.3, 130.52, 130.46, 130.4, 129.8, 126.9, 125.2, 120.3, 116.7, 111.9, 82.0, 73.4, 66.1, 64.7, 55.9, 27.7, 18.0 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{29}H_{23}ClN_5O_2$ $[M + H]^+$ 508.1535, found 508.1536.

(2'*R*,3*R*,3'*S*)-4'-Amino-5-bromo-1,3''-dimethyl-2,5''-dioxo-1'',2'-diphenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ha). From 29.0 mg (0.10 mmol) **1h** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ha** as a

light pink solid (47.0 mg, 85% yield), mp 148–150 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 12.5 min (minor), t_R = 15.1 min (major); >99% *ee*. $[\alpha]_D^{20}$ = +8.8 (*c* = 1.22, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.83–7.80 (m, 2H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.51 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.40–7.35 (m, 2H), 7.19–7.11 (m, 4H), 7.05–7.02 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.81 (br s, 2H), 4.47 (s, 1H), 3.11 (s, 3H), 2.70 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 177.6, 173.7, 161.3, 161.1, 144.8, 139.8, 134.7, 134.3, 134.0, 130.52, 130.47, 130.4, 127.9, 126.9, 120.3, 117.1, 116.7, 112.4, 82.0, 73.4, 66.1, 64.7, 55.9, 27.7, 18.0 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{29}H_{23}BrN_5O_2$ $[M + H]^+$ 552.1030, found 552.1032.

(2'*R*,3*R*,3'*S*)-4'-Amino-6-chloro-1,3''-dimethyl-2,5''-dioxo-1'',2'-diphenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ia). From 24.6 mg (0.10 mmol) **1i** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ia** as a white solid (45.7 mg, 90% yield), mp 102–104 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 88:12, flow rate 1.0 mL/min, detection at 254 nm): t_R = 28.8 min (minor), t_R = 30.9 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –93.3 (*c* = 2.12, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.83–7.80 (m, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.39–7.35 (m, 2H), 7.25 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.19–7.10 (m, 4H), 7.02–6.99 (m, 3H), 6.78 (br s, 2H), 4.48 (s, 1H), 3.13 (s, 3H), 2.71 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 178.0, 173.8, 161.4, 161.0, 146.8, 139.9, 136.5, 134.0, 131.0, 130.5, 130.44, 130.43, 130.35, 126.9, 126.4, 124.8, 120.3, 116.7, 111.0, 82.1, 73.3, 66.1, 64.3, 27.8, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{29}H_{23}ClN_5O_2$ $[M + H]^+$ 508.1535, found 508.1537.

(2'*R*,3*R*,3'*S*)-4'-Amino-1,3''-dimethyl-2,5''-dioxo-1'',2'-diphenyl-7-(trifluoromethyl)-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ja). From 33.5 mg (0.10 mmol) **1j** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ja**

as a light yellow solid (48.2 mg, 89% yield), mp 113–115 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 7.9 min (minor), t_R = 9.9 min (major); 98% *ee*. $[\alpha]_D^{20}$ = –126.0 (*c* = 1.81, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.85 (d, *J* = 6.8 Hz, 1H), 7.83–7.80 (m, 2H), 7.70 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.40–7.35 (m, 2H), 7.20–7.11 (m, 4H), 6.97–6.94 (m, 2H), 6.88 (br s, 2H), 4.47 (s, 1H), 3.25 (q, *J* = 2.4 Hz, 3H), 2.74 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 179.1, 173.6, 161.5, 161.3, 143.2, 139.8, 135.2, 133.6, 130.6, 130.54, 130.46, 130.3, 129.3, 129.2 (q, *J* = 5.9 Hz), 126.9, 125.4 (q, *J* = 270.9 Hz), 125.1, 120.3, 116.6, 113.6 (q, *J* = 32.9 Hz), 81.5, 73.2, 67.0, 63.4, 30.3 (q, *J* = 6.1 Hz), 18.2 ppm. ^{19}F{^{1}H} NMR (377 MHz, acetone-d6): δ –53.8 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{30}H_{23}F_3N_5O_2$ $[M + H]^+$ 542.1798, found 542.1795.

(2'*R*,3*R*,3'*S*)-4'-Amino-1,3'',5,7-tetramethyl-2,5''-dioxo-1'',2'-diphenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ka). From 23.9 mg (0.10 mmol) **1k** and 31.5 mg (0.12 mmol) unsaturated pyrazolinone **2a**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ka** as a white solid (46.6 mg, 93% yield), mp 134–136 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 10.1 min (minor), t_R = 12.5 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –80.3 (*c* = 1.20, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.83–7.81 (m, 2H), 7.40–7.35 (m, 2H), 7.19–7.08 (m, 5H), 7.03–7.00 (m, 2H), 6.87 (s, 1H), 6.63 (br s, 2H), 4.47 (s, 1H), 3.36 (s, 3H), 2.69 (s, 3H), 2.44 (s, 3H), 2.34 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 178.6, 174.1, 161.7, 160.5, 140.8, 139.9, 135.4, 134.6, 134.4, 133.1, 130.5, 130.4, 130.3, 130.2, 126.8, 123.5, 121.6, 120.3, 117.0, 83.6, 73.5, 66.4, 64.0, 21.9, 19.6, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{31}H_{28}N_5O_2$ $[M + H]^+$ 502.2238, found 502.2241.

(2'*R*,3*R*,3'*S*)-4'-Amino-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-2'-(p-tolyl)-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ab). From 21.1 mg (0.10

mmol) **1a** and 33.1 mg (0.12 mmol) unsaturated pyrazolinone **2b**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ab** as a light pink solid (46.3 mg, 95% yield), mp 120–122 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 19.8 min (minor), t_R = 14.9 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –122.7 (*c* = 2.14, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.84–7.82 (m, 2H), 7.53 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.39–7.35 (m, 2H), 7.32 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.21 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.18–7.14 (m, 1H), 6.92–6.88 (m, 5H), 6.69 (br s, 2H), 4.49 (s, 1H), 3.11 (s, 3H), 2.71 (s, 3H), 2.10 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 178.1, 174.0, 161.6, 160.8, 145.5, 140.0, 139.9, 132.4, 131.3, 131.0, 130.5, 130.3, 126.8, 125.05, 124,99, 120.2, 116.9, 110.3, 82.9, 73.6, 66.0, 64.6, 27.6, 21.8, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{30}H_{26}N_5O_2$ $[M + H]^+$ 488.2081, found 488.2074.

(2'*R*,3*R*,3'*S*)-4'-Amino-2'-(4-methoxyphenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ac). From 21.1 mg (0.10 mmol) **1a** and 35.1 mg (0.12 mmol) unsaturated pyrazolinone **2c**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ac** as a white solid (48.3 mg, 96% yield), mp 89–91 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 70:30, flow rate 1.0 mL/min, detection at 254 nm): t_R = 11.0 min (minor), t_R = 9.1 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –136.9 (*c* = 2.98, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.84–7.81 (m, 2H), 7.53 (dd, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H), 7.38–7.34 (m, 2H), 7.31 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.21 (td, J_1 = 7.4 Hz, J_2 = 0.9 Hz, 1H), 7.18–7.13 (m, 1H), 6.97–6.94 (m, 2H), 6.87 (d, J = 7.6 Hz, 1H), 6.68 (br s, 2H), 6.64–6.60 (m, 2H), 4.46 (s, 1H), 3.58 (s, 3H), 3.09 (s, 3H), 2.73 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 178.1, 174.0, 161.6, 161.5, 160.8, 145.4, 139.9, 132.4, 131.8, 131.3, 130.5, 126.8, 125.8, 125.03, 124.95, 120.2, 116.9, 115.5, 110.3, 82.7, 73.6, 66.0, 64.7, 56.2, 27.6, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{30}H_{26}N_5O_3$ $[M + H]^+$ 504.2030, found 504.2027.

(2'*R*,3*R*,3'*S*)-4'-Amino-2'-(4-fluorophenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydro-dispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ad). From 21.1 mg (0.10 mmol) **1a** and 33.6 mg (0.12 mmol) unsaturated pyrazolinone **2d**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ad** as a light yellow solid (46.2 mg, 94% yield), mp 113–115 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 20.6 min (minor), t_R = 15.7 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –115.7 (*c* = 1.94, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.82–7.80 (m, 2H), 7.54 (dd, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H), 7.40–7.32 (m, 3H), 7.23 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.19–7.15 (m, 1H), 7.09–7.05 (m, 2H), 6.92–6.87 (m, 3H), 6.73 (br s, 2H), 4.50, (s, 1H), 3.11 (s, 3H), 2.73 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 177.9, 173.8, 164.4 (d, *J* = 245.7 Hz), 161.4, 160.7, 145.4, 139.8, 132.7 (d, *J* = 8.4 Hz), 132.1, 131.4, 130.5, 130.4 (d, *J* = 3.5 Hz), 126.9, 125.2, 125.0, 120.3, 117.1 (d, *J* = 20.9 Hz), 116.8, 110.4, 82.6, 73.4, 65.7, 64.7, 27.6, 18.0 ppm. ^{19}F{^{1}H} NMR (377 MHz, acetone-d6): δ –114.6 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{29}H_{23}FN_5O_2$ $[M + H]^+$ 492.1830, found 492.1822.

(2'*R*,3*R*,3'*S*)-4'-Amino-2'-(4-chlorophenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydro-dispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ae). From 21.1 mg (0.10 mmol) **1a** and 35.6 mg (0.12 mmol) unsaturated pyrazolinone **2e**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ae** as a light yellow solid (49.3 mg, 97% yield), mp 102–104 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 31.1 min (minor), t_R = 16.6 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –102.0 (*c* = 2.08, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.83–7.80 (m, 2H), 7.54 (dd, J_1 = 7.4 Hz, J_2 = 0.6 Hz, 1H), 7.40–7.32 (m, 3H), 7.31 (td, J_1 = 7.4 Hz, J_2 = 0.9 Hz, 1H), 7.19–7.14 (m, 3H), 7.05–7.01 (m, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.75 (br s, 2H), 4.49 (s, 1H), 3.13 (s, 3H), 2.72 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 177.8, 173.8, 161.3, 160.6, 145.4, 139.8,

135.8, 133.2, 132.2, 132.0, 131.5, 130.53, 130.46, 126.9, 125.2, 125.0, 120.3, 116.7, 110.5, 82.7, 73.3, 65.5, 64.5, 27.6, 18.0 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{29}H_{23}ClN_5O_2$ $[M + H]^+$ 508.1535, found 508.1534.

(2'*R*,3*R*,3'*S*)-4'-Amino-2'-(4-bromophenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3af). From 21.1 mg (0.10 mmol) **1a** and 40.9 mg (0.12 mmol) unsaturated pyrazolinone **2f**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3af** as a light yellow solid (49.8 mg, 90% yield), mp 118–120 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 36.3 min (minor), t_R = 18.0 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –109.3 (*c* = 2.09, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.83–7.80 (m, 2H), 7.54 (dd, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H), 7.40–7.30 (m, 5H), 7.23 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.20–7.16 (m, 1H), 6.98–6.96 (m, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.75 (br s, 2H), 4.48 (s, 1H), 3.13 (s, 3H), 2.72 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 177.8, 173.8, 161.3, 160.6, 145.4, 139.8, 133.7, 133.5, 132.5, 132.0, 131.5, 130.5, 126.9, 125.2, 125.0, 124.1, 120.3, 116.7, 110.5, 82.7, 73.3, 65.5, 64.5, 27.6, 18.0 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{29}H_{23}BrN_5O_2$ $[M + H]^+$ 552.1030, found 552.1031.

(2'*R*,3*R*,3'*S*)-4'-Amino-2'-(2-methoxyphenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ag). From 21.1 mg (0.10 mmol) **1a** and 35.1 mg (0.12 mmol) unsaturated pyrazolinone **2g**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ag** as a light pink solid (48.9 mg, 97% yield), mp 162–164 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 25.0 min (minor), t_R = 31.8 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –109.3 (*c* = 2.09, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.90–7.87 (m, 2H), 7.53 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.46 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.41–7.36 (m, 2H),

7.29 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.19–7.13 (m, 2H), 7.11–7.07 (m, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.78 (td, J_1 = 7.8 Hz, J_2 = 0.9 Hz, 1H), 6.66 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H), 6.56 (br s, 2H), 5.22 (s, 1H), 3.30 (s, 3H), 3.19 (s, 3H), 2.48 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, acetone-d6): δ178.9, 174.3, 161.0, 160.9, 159.6, 145.4, 140.4, 132.3, 131.1, 130.5, 130.2, 126.3, 125.5, 124.8, 123.2, 121.9, 119.8, 116.9, 112.6, 110.2, 83.3, 80.2, 72.6, 64.1, 56.8, 55.3, 27.7, 17.9 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{30}H_{26}N_5O_3$ $[M + H]^+$ 504.2030, found 504.2024.

(2'*R*,3*R*,3'*S*)-4'-Amino-2'-(3-bromophenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ah). From 21.1 mg (0.10 mmol) **1a** and 40.9 mg (0.12 mmol) unsaturated pyrazolinone **2h**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ah** as a light yellow solid (50.3 mg, 91% yield), mp 243–245 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R = 10.5 min (minor), t_R = 13.1 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –102.1 (c = 1.35, acetone). ^1H NMR (400 MHz, acetone-d6): δ7.84–7.81 (m, 2H), 7.55 (dd, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H), 7.42–7.34 (m, 4H), 7.26–7.17 (m, 3H), 7.10 (t, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.76 (br s, 2H), 4.48 (s, 1H), 3.15 (s, 3H), 2.70 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, acetone-d6): δ177.8, 173.7, 161.2, 160.5, 145.3, 139.8, 137.0, 133.4, 133.1, 132.4, 131.9, 131.6, 130.6, 129.4, 127.0, 125.3, 125.1, 123.8, 120.4, 116.7, 110.6, 82.7, 73.2, 65.1, 64.4, 27.6, 18.0 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{29}H_{23}BrN_5O_2$ $[M + H]^+$ 552.1030, found 552.1033.

(2'*R*,3*R*,3'*S*)-4'-Amino-2'-(3-methoxyphenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ai). From 21.1 mg (0.10 mmol) **1a** and 35.1 mg (0.12 mmol) unsaturated pyrazolinone **2i**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ai** as a light yellow solid (42.6 mg, 85% yield), mp 140–142 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-

propanol = 70:30, flow rate 1.0 mL/min, detection at 254 nm): t_R = 16.9 min (minor), t_R = 14.3 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –119.2 (*c* = 1.84, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.86–7.83 (m, 2H), 7.54 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.41–7.37 (m, 2H), 7.33 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.22 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.20–7.15 (m, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.70–6.68 (m, 3H), 6.62 (t, *J* = 2.0 Hz, 1H), 6.54 (dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 4.53 (s, 1H), 3.56 (s, 3H), 3.14 (s, 3H), 2.70 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 178.1, 173.9, 161.6, 161.4, 160.7, 145.5, 139.9, 135.9, 132.4, 131.4, 130.5, 126.8, 125.1, 125.0, 122.4, 120.3, 116.8, 115.9, 115.3, 110.4, 82.9, 73.4, 65.6, 64.4, 56.3, 27.6, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{30}H_{26}N_5O_3$ $[M + H]^+$ 504.2030, found 504.2036.

(2'*R*,3*R*,3'*S*)-4'-Amino-2'-(3,4-dimethoxyphenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3aj). From 21.1 mg (0.10 mmol) **1a** and 38.7 mg (0.12 mmol) unsaturated pyrazolinone **2j**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3aj** as a light yellow solid (46.8 mg, 88% yield), mp 140–142 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R = 23.1 min (minor), t_R = 25.3 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –127.2 (*c* = 1.81, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.40–7.36 (m, 2H), 7.33 (td, J_1 = 7.8 Hz, J_2 = 0.9 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.71–6.69 (m, 3H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.46 (dd, J_1 = 8.2 Hz, J_2 = 2.2 Hz, 1H), 4.47 (s, 1H), 3.61 (s, 3H), 3.55 (s, 3H), 3.15 (s, 3H), 2.73 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 178.3, 174.1, 161.7, 160.8, 151.2, 150.7, 145.5, 140.0, 132.5, 131.3, 130.5, 126.8, 126.3, 125.1, 125.0, 123.0, 120.2, 116.9, 113.3, 113.0, 110.4, 82.8, 73.6, 66.1, 64.6, 56.7, 56.6, 27.6, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{31}H_{28}N_5O_4$ $[M + H]^+$ 534.2136, found 534.2130.

(2'*R*,3*R*,3'*S*)-4'-Amino-2'-(furan-2-yl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydro-dispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3ak). From 21.1 mg (0.10 mmol) **1a** and 30.3 mg (0.12 mmol) unsaturated pyrazolinone **2k**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3ak** as a light yellow solid (41.8 mg, 90% yield), mp 91–93 °C. HPLC (Daicel Chiralpak IB, *n*-hexane/2-propanol = 95:5, flow rate 1.0 mL/min, detection at 254 nm): t_R = 41.1 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –116.5 (*c* = 1.94, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.40–7.36 (m, 1H), 7.25–7.20 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.69 (br s, 2H), 6.20–6.19 (m, 1H), 6.03 (d, *J* = 3.2 Hz, 1H), 4.59 (s, 1H), 3.24 (s, 3H), 2.48 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 177.3, 173.6, 161.5, 160.2, 148.9, 145.7, 144.6, 140.1, 132.2, 131.6, 130.6, 126.8, 125.1, 125.0, 120.3, 116.6, 112.3, 110.4, 109.6, 82.6, 71.6, 62.6, 57.4, 27.7, 17.7 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{27}H_{22}N_5O_3$ $[M + H]^+$ 464.1717, found 464.1712.

(2'*R*,3*R*,3'*S*)-4'-Amino-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-2'-(thiophen-2-yl)-1'',5''-dihydro-dispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3al). From 21.1 mg (0.10 mmol) **1a** and 32.2 mg (0.12 mmol) unsaturated pyrazolinone **2l**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3al** as a white solid (40.8 mg, 85% yield), mp 121–123 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 22.2 min (minor), t_R = 25.9 min (major); 99% *ee*. $[\alpha]_D^{20}$ = –139.0 (*c* = 1.54, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.89–7.87 (m, 2H), 7.51 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.43–7.34 (m, 3H), 7.25–7.17 (m, 3H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.79–6.73 (m, 4H), 4.77 (s, 1H), 3.16 (s, 3H), 2.67 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 177.6, 173.7, 161.4, 160.4, 145.8, 139.9, 135.5, 132.0, 131.6, 130.6, 128.8, 128.7, 127.8, 126.9, 125.2, 125.0, 120.3, 116.7, 110.5, 82.6, 73.3, 64.6, 60.5, 27.7, 18.2 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{27}H_{22}N_5O_2S$ $[M + H]^+$ 480.1489, found 480.1481.

(2'*R*,3*R*,3'*S*)-4'-Amino-1,3''-dimethyl-2,5''-dioxo-2'-phenyl-1''-(p-tolyl)-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3am). From 21.1 mg (0.10 mmol) **1a** and 33.2 mg (0.12 mmol) unsaturated pyrazolinone **2m**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3am** as a light pink solid (46.5 mg, 95% yield), mp 85–87 °C. HPLC (Daicel Chiralpak IB, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 13.7 min (minor), t_R = 10.4 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –137.5 (*c* = 2.03, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.70–7.67 (m, 2H), 7.54 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.32 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.23–7.17 (m, 3H), 7.13–7.07 (m, 3H), 7.01–6.99 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.68 (br s, 2H), 4.52 (s, 1H), 3.10 (s, 3H), 2.69 (s, 3H), 2.29 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 178.0, 173.6, 161.4, 160.8, 145.4, 137.5, 136.4, 134.4, 132.3, 131.3, 130.9, 130.34, 130.31, 130.2, 125.1, 125.0, 120.4, 116.9, 110.3, 82.8, 73.4, 66.1, 64.5, 27.6, 21.8, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{30}H_{26}N_5O_2$ $[M + H]^+$ 488.2081, found 488.2073.

(2'*R*,3*R*,3'*S*)-4'-Amino-1''-(4-chlorophenyl)-1,3''-dimethyl-2,5''-dioxo-2'-phenyl-1'',5''-dihydrodispiro[indoline-3,1'-cyclopentane-3',4''-pyrazol]-4'-ene-5'-carbonitrile (3an). From 21.1 mg (0.10 mmol) **1a** and 35.6 mg (0.12 mmol) unsaturated pyrazolinone **2n**, purified by silica gel (200-300 mesh) column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1 v/v) as eluent to obtain **3an** as a light yellow solid (49.3 mg, 97% yield), mp 79–81 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 27.7 min (minor), t_R = 17.4 min (major); >99% *ee*. $[\alpha]_D^{20}$ = –142.5 (*c* = 2.25, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 7.85–7.83 (m, 2H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.43–7.40 (m, 2H), 7.32 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.22 (td, J_1 = 7.2 Hz, J_2 = 0.7 Hz, 1H), 7.14–7.08 (m, 3H), 7.02–7.00 (m, 2H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.71(br s, 2H), 4.51 (s, 1H), 3.10 (s, 3H), 2.72 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 177.9, 174.0, 162.1, 160.5, 145.4, 138.6, 134.2, 132.2, 131.39, 131.37, 130.5, 130.4, 130.3, 125.1, 125.0, 121.7, 116.8, 110.4, 82.9, 73.5,

66.2, 64. 5, 27.6, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{29}H_{23}ClN_5O_2$ $[M + H]^+$ 508.1535, found 508.1529.

Synthesis of compound 4aa

The compound **4aa** were prepared by modified reported procedure.[15] The corresponding chiral compound **3aa** (47.4 mg，0.1 mmol) was dissolved in 1.0 mL Ac_2O and 0.5 mL pyridine, and then stirred for about 24 h at 90 °C. When the reaction was completed, the solution was concentrated under vacuum. The residue was then dissolved in dry CH_2Cl_2, and washed with water several times. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified via flash chromalography (eluent: petroleum ether/ethyl acetate = 4/1 to 3/1 v/v) to give compound **4aa**.

(3*R*,6'*R*,7'*S*)-1,2',3''-Trimethyl-1''-phenyl-6'-(p-tolyl)-6'*H*-dispiro[indoline-3,5'-cyclopenta[d]pyrimidine-7',4''-pyrazole]-2,4',5''(1''*H*,3'*H*)-trione (4aa). White solid (29.5 mg, 57% yield), mp 154–156 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R = 34.8 min (minor), t_R = 10.4 min (major); 99% *ee*. $[\alpha]_D^{20}$ = –248.4 (*c* = 1.25, acetone). ^{1}H NMR (400 MHz, acetone-d6): δ 10.02 (s, 1H), 7.64–7.61 (m, 2H), 7.52 (dd, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H, 1H), 7.36–7.29 (m, 3H), 7.23 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.16–7.06 (m, 6H), 6.89 (d, J = 7.6 Hz, 1H), 4.40 (s, 1H), 3.10 (s, 3H), 2.64 (s, 3H), 2.15 (s, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, acetone-d6): δ 176.3, 175.0, 170.2, 159.7, 151.9, 145.6, 140.2, 133.2, 131.9, 131.2, 130.8, 130.7, 130.3, 130.1, 126.6, 125.4, 125.0, 120.9, 114.6, 110.7, 99.1, 72.4, 69.0, 64.1, 27.8, 24.5, 18.1 ppm. HRMS (ESI-TOF): *m/z* calcd. for $C_{31}H_{26}N_5O_3$ $[M + H]^+$ 516.2030, found 516.2018.

ASSOCIATED CONTENT

Supporting Information

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

Copies of ^{1}H, ^{13}C, ^{19}F NMR and HPLC spectra for the products.

Single crystal X-ray crystallography data for product **3af**.

AUTHOR INFORMATION

Corresponding Author

*Fax: (+86)-010-68914985; E-mail: dudm@bit.edu.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful for financial support from the National Postdoctoral Program for Innovative Talents of China (No. BX201700030) and the Project funded by China Postdoctoral Science Foundation (No. 2017M620630). We also thank Analysis & Testing Center of Beijing Institute of Technology for the measurement of NMR and mass spectrometry.

REFERENCES

(1) For recent reviews on spirocyclic compounds, see: (a) Kotha, S.; Panguluri, N. R.; Ali, R. Design and Synthesis of Spirocycles. *Eur. J. Org. Chem.* **2017**, *2017*, 5316. (b) Reddy, C. R.; Prajapti, S. K.; Warudikar, K.; Ranjan, R.; Rao, B. B. *ipso*-Cyclization: an Emerging Tool for Multifunctional Spirocyclohexadienones. *Org. Biomol. Chem.* **2017**, *15*, 3130. (c) James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Synthesis of Spirocyclic Indolenines. *Chem. –Eur. J.* **2016**, *22*, 2856. (d) Cao, Z.-Y.; Zhou, J. Catalytic Asymmetric Synthesis of Polysubstituted Spirocyclopropyl Oxindoles: Organocatalysis

versus Transition Metal Catalysis. *Org. Chem. Front.* **2015**, *2*, 849. (e) Carreira, E. M.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257. (f) Rios, R. Enantioselective Methodologies for the Synthesis of Spiro Compounds. *Chem. Soc. Rev.* **2012**, *41*, 1060.

(2) (a) Schmidt, B.; Scheufler, C.; Volz, J.; Feth, M. P.; Hummel, R.-P.; Hatzelmann, A.; Zitt, C.; Wohlsen, A.; Marx, D.; Kley, H.-P.; Ockert, D.; Heuser, A.; Christiaans, J. A. M.; Sterk, G. J.; Menge, W. M. P. B. Pyrazolone Derivatives as PDE4 Inhibitors. Germany Patent WO2008138939, 2010. (b) Schlemminger, I.; Schmidt, B.; Flockerzi, D.; Tenor, H.; Zitt, C.; Hatzelmann, A.; Marx, D.; Braun, C.; Kuelzer, R.; Heuser, A.; Kley, H.-P.; Sterk, G. J. Novel Pyrazolone-Derivatives and Their Use as PD4 Inhibitors. Germany Patent WO2010055083, 2008. (c) Chande, M. S.; Barve, P. A.; Suryanarayan, V. Synthesis and Antimicrobial Activity of Novel Spirocompounds with Pyrazolone and Pyrazolthione Moiety. *J. Heterocycl. Chem*. **2007**, *44*, 49.

(3) (a) Samineni, R.; Madapa, J.; Pabbaraja, S.; Mehta, G. Stitching Oxindoles and Ynones in a Domino Process: Access to Spirooxindoles and Application to a Short Synthesis of Spindomycin B. *Org. Lett.* **2017**, *19*, 6152. (b) Ribeiro, C. J. A.; Amaral, J. D.; Rodrigues, C. M. P.; Moreira R.; Santos, M. M. M. Spirooxadiazoline Oxindoles with Promising in Vitro Antitumor Activities. *Med. Chem. Commun.* **2016**, *7*, 420. (c) Bian, Z.; Marvin, C. C.; Pettersson, M.; Martin, S. F. Enantioselective Total Syntheses of Citrinadins A and B. Stereochemical Revision of Their Assigned Structures. *J. Am. Chem. Soc.* **2014**, *136*, 14184. (d) Trost, B. M.; Bringley, D. A.; Zhang, T.; Cramer, N. Rapid Access to Spirocyclic Oxindole Alkaloids: Application of the Asymmetric Palladium-Catalyzed [3 + 2] Trimethylenemethane Cycloaddition. *J. Am. Chem. Soc.* **2013**, *135*, 16720. (e) Ding, Y.; Gruschow, S.; Greshock, T. J.; Finefield, J. M.; Sherman, D. H.; Williams, R. M. Detection of VM55599 and Preparaherquamide from *Aspergillus japonicus* and *Penicillium fellutanum*: Biosynthetic Implications. *J. Nat. Prod.* **2008**, *71*, 1574. (f) Mugi-

shima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. Absolute Stereochemistry of Citrinadins A and B from Marine-Derived Fungus. *J. Org. Chem.* **2005**, *70*, 9430.

(4) (a) Mandha, S. R.; Siliveri, S.; Alla, M.; Bommena, V. R.; Bommineni, M. R.; Balasubramanian, S. Eco-friendly Synthesis and Biological Evaluation of Substituted Pyrano [2, 3-*c*] pyrazoles. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5272. (b) Janin, Y. L. Antituberculosis drugs: ten years of research. *Bioorg. Med. Chem.* **2007**, *15*, 2479. (c) Wamhoff, H.; Kroth, E.; Strauch, K. Dihalogentriphenylphosphorane in der Heterocyclensynthese; 27[1]: Heterokondensierte 1, 2, 4-Triazolo [1, 5-*c*] pyrimidine aus Enaminonitrilen via *O*-Ethylformimide. *Synthesis* **1993**, *1993*, 1129.

(5) For a review on the biological activity study of spiro-oxindole pyrazolones, see: Das, D.; Banerjee R.; Mitra, A. Bioactive and Pharmacologically Important Pyrano [2, 3-*c*] pyrazoles. *J. Chem. Pharm. Res.* **2014**, *6*, 108.

(6) For selected reviews, see: (a) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas III, C. F. Organocatalytic Asymmetric Assembly Reactions: Synthesis of Spirooxindoles via Organocascade Strategies. *ACS Catal.* **2014**, *4*, 743. (b) Hong, L.; Wang, R. Recent Advances in Asymmetric Organocatalytic Construction of 3, 3'-Spirocyclic Oxindoles. *Adv. Synth. Catal.* **2013**, *355*, 1023. (c) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. Recent Advances in Organocatalytic Methods for the Synthesis of Disubstituted 2-and 3-Indolinones. *Chem. Soc. Rev.* **2012**, *41*, 7247. (d) Galliford, C. V.; Scheidt, K. A. Pyrrolidinyl-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (e) Chauhan, P.; Mahajan, S.; Enders, D. Asymmetric Synthesis of Pyrazoles and Pyrazolones Employing the Reactivity of Pyrazolin-5-one Derivatives. *Chem. Commun.* **2015**, *51*, 12890. For selected examples, see: (f) Zhao, J.-Q.; Yang, L.; Zhou, X.-J.; You, Y.; Wang, Z.-H.; Zhou, M.-Q.; Zhang, X.-M.; Xu, X.-Y.; Yuan, W.-C. Organocatalyzed Dearomative Cycloaddition of 2-Nitrobenzofurans and Isatin-Derived Morita–Baylis–Hillman Carbonates: Highly Stereoselective Construction of Cyclopenta [*b*] benzofuran Scaffolds. *Org. Lett.* **2019**, *21*, 660. (g) Wang, C.-C.; Huang, J.; Li, X.-H.; Kramer, S.; Lin

G.-Q. Asymmetric Organocatalytic [4 + 1] Annulations: Enantioselective Construction of Multifunctionalized Spirocyclopentane Oxindoles Bearing α, α-Disubstituted α-Amino-β-keto Esters. *Org. Lett*. **2018**, *20*, 2888. (h) Guo, J.-M.; Bai, X.-G.; Wang, Q.-L.; Bu, Z.-W. Diastereoselective Construction of Indole-Bridged Chroman Spirooxindoles through a TfOH-Catalyzed Michael Addition-Inspired Cascade Reaction. *J. Org. Chem.* **2018**, *83*, 3679. (i) Zhu, Y. S.; Guo, J.; Jin, S.-J.; Guo, J.-M.; Bai, X.-G.; Wang, Q.-L.; Bu, Z.-W. Construction of Bridged Cyclic *N*, *O*-ketal Spirooxindoles Through a Michael Addition/*N*, *O*-ketalization Sequence. *Org. Biomol. Chem*., **2018**, *16*, 1751. (j) Zhu, Y.-S.; Zhou, J.; Jin, S.-J., Dong, H.-H., Guo, J.-M., Bai, X.-G., Wang, Q.-L.; Bu, Z.-W. Metal-free Diastereoselective Construction of Bridged Ketal Spirooxindoles via a Michael Addition-Inspired Sequence. *Chem. Commun*., **2017**, *53*, 11201. (k) Zhu, Y.-S.; Yuan, B.-B.; Guo, J.-M.; Jin, S.-J.; Dong, H.-H.; Wang, Q.-L.; Bu, Z.-W. A Copper-Catalyzed Friedel–Crafts Alkylation/Cyclization Sequence: an Approach to Functionalized Pyrrolo [1, 2-*a*] indole Spirooxindoles and 9 *H*-Pyrrolo [1, 2-*a*] indoles. *J. Org. Chem*. **2017**, *82*, 5669. (l) Zhu, Y.-S.; Wang, W.-B.; Yuan, B.-B.; Li, Y.-N.; Wang, Q.-L.; Bu, Z.-W. A DBU-Catalyzed Michael–Pinner–Isomerization Cascade Reaction of 3-Hydroxyoxindoles with Isatylidene Malononitriles: Access to Highly Functionalized Bispirooxindoles Containing a Fully Substituted Dihydrofuran Motif. *Org. Biomol. Chem.*, **2017**, *15*, 984. (m) Zhao, X.; Liu, X.; Xiong, Q.; Mei, H.; Ma, B.; Lin, L.; Feng, X. The Asymmetric Synthesis of Polycyclic 3-Spirooxindole Alkaloids via the Cascade Reaction of 2-Isocyanoethylindoles. *Chem. Commun.* **2015**, *51*, 16076. (n) Wang, L.; Li, S.; Blümel, M.; Puttreddy, R.; Peuronen, A.; Rissanen, K.; Enders, D. Switchable Access to Different Spirocyclopentane Oxindoles by *N*-Heterocyclic Carbene Catalyzed Reactions of Isatin-Derived Enals and *N*-Sulfonyl Ketimines. *Angew. Chem., Int. Ed.* **2017**, *56*, 8516. (o) Zheng, J.; Wang, S.-B.; Zheng, C.; You, S.-L. Asymmetric Synthesis of Spiropyrazolones by Rhodium-Catalyzed C(sp^2)−H Functionalization/Annulation Reactions. *Angew. Chem., Int. Ed.* **2017**, *56*, 4540. (p) Yang, W.-J.; Sun, W.; Zhang, C.; Wang, Q.-J.; Guo, Z.-Y.; Mao, B.-M.; Liao, J.-N.; Guo, H.-C. Lewis-Base-Catalyzed Asymmetric [3 + 3] Annulation Reaction of Morita–Baylis–Hillman Carbonates: Enantioselective Synthesis of Spirocyclohexenes. *ACS Catal.* **2017**, *7*, 3142. (q) Wang,

S.-L.; Izquierdo, J.; Rodríguez-Escrich, C.; Pericàs, M. A. Asymmetric [4 + 2] Annulation Reactions Catalyzed by a Robust, Immobilized Isothiourea. *ACS Catal.* **2017**, *7*, 2780. (r) Kumarswamyreddy, N.; Kesavan, V. Enantioselective Synthesis of Dihydrospiro[indoline-3,4'-pyrano[2,3-c]pyrazole] Derivatives via Michael/Hemiketalization Reaction. *Org. Lett.* **2016**, *18*, 1354. (s) Xie, J.; Xing, X.-Y.; Sha, F.; Wu, Z.-Y.; Wu, X.-Y. Enantioselective Synthesis of Spiro [indoline-3, 4'-pyrano [2, 3-c] pyrazole] Derivatives via an Organocatalytic Asymmetric Michael/Cyclization Cascade Reaction. *Org. Biomol. Chem.* **2016**, *14*, 8346.

(7) Chen, Q.; Liang, J.-Y.; Wang, S.-L.; Wang, D.; Wang, R. An Asymmetric Approach toward Chiral Multicyclic Spirooxindoles from Isothiocyanato Oxindoles and Unsaturated Pyrazolones by a Chiral Tertiary Amine Thiourea Catalyst. *Chem. Commun.* **2013**, *49*, 1657.

(8) Cui, B.-D.; Li, S.-W.; Zuo, J.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. Quinine-Catalyzed Asymmetric Domino Michael-Cyclization Reaction for the Synthesis of Spirocyclic Oxindoles Bearing Two Spiro Quaternary Centers and Three Consecutive Stereocenters. *Tetrahedron* **2014**, *70*, 1895.

(9) Bao, X.-Z.; Wei, S.-Q.; Qian, X.-K.; Qu, J.-P.; Wang, B.-M.; Zou, L.-W.; Ge, G.-B. Asymmetric Construction of a Multi-Pharmacophore-Containing Dispirotriheterocyclic Scaffold and Identification of a Human Carboxylesterase 1 Inhibitor. *Org. Lett.* **2018**, *20*, 3394.

(10) Liu, X.-L.; Zuo, X.; Wang, J.-X.; Chang, S.-Q.; Wei, Q.-D.; Zhou, Y. A Bifunctional Pyrazolone-Chromone Synthon Directed Organocatalytic Double Michael Cascade Reaction: Forging Five Stereocenters in Structurally Diverse Hexahydroxanthones. *Org. Chem. Front.* **2019**, *6*, 1485.

(11) Li, J.-H.; Feng, T.-F.; Du, D.-M. Construction of Spirocyclopropane-Linked Heterocycles Containing Both Pyrazolones and Oxindoles through Michael/Alkylation Cascade Reactions. *J. Org. Chem.* **2015**, *80*, 11369.

(12) Zhu, X.-Q.; Wu, J.-S.; Xie, J.-W. Stereoselective Construction of Bi-Spirooxindole Frameworks via a Michael Addition/Cyclization and an Unexpected Redox/Oxidative Coupling/Cyclization. *Tetrahedron* **2016**, *72*, 8327.

(13) Zhao, B.-L.; Lin, Y.; Du, D.-M. Enantioselective Construction of Bispirooxindoles via Squaramide-Catalysed Cascade Michael/Cyclization Reaction. *Adv. Synth. Catal.* **2019**, *361*, 3387.

(14) For selected review, see: Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. Bifunctional Amine-Squaramides: Powerful Hydrogen-Bonding Organocatalysts for Asymmetric Domino/Cascade Reactions. *Adv. Synth. Catal.* **2015**, *357*, 253.

(15) For selected examples, see: (a) Manoni, F.; Connon, S. J. Catalytic Asymmetric Tamura Cycloadditions. *Angew. Chem., Int. Ed.* 2014, *53*, 2628. (b) Akula, P. S.; Hong, B. C.; Lee, G. H. Catalyst- and Substituent-Controlled Switching of Chemoselectivity for the Enantioselective Synthesis of Fully Substituted Cyclobutane Derivatives via 2 + 2 Annulation of Vinylogous Ketone Enolates and Nitroalkene. *Org. Lett.* **2018**, *20*, 7835. (c) Mukhopadhyay, S.; Pan, S. C. Organocatalytic Asymmetric Synthesis of 2, 5-Disubstituted Oxazolidines. *Adv. Synth. Catal.* **2018**, *361*, 1028. (d) Zhang, Y.-P.; You, Y.; Zhao, J.-Q.; Zhang, X.-M.; Xu, X.-Y.; Yuan, W.-C. Chiral Bifunctional Amine-Squaramide Catalyzed Highly Diastereo- and Enantioselective Michael/Aldol Cascade Reaction of 2-Mercaptobenzaldehyde and *α*, *β*-Unsaturated 7-Azaindoline Amides. *J. Org. Chem.* **2019**, *84*, 7984.

(16) (a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Catalysts. *J. Am. Chem. Soc.* **2008**, *130*, 14416. (b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. Squaramides: Bridging from Molecular Recognition to Bifunctional Organocatalysis. *Chem. - Eur. J.* **2011**, *17*, 6890. (c) Lu, T.; Wheeler, S. E. Origin of the Superior Performance of (Thio)Squaramides over (Thio)Ureas in Organocatalysis. *Chem. - Eur. J.* **2013**, *19*, 15141.

(17) CCDC 1911117 (for **3af**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(18) (a) Chen, X.; Qi, Z.-H.; Zhang, S.-Y.; Kong, L.-P.; Wang, Y.; Wang, X.-W. Enantioselective Construction of Functionalized Thiopyrano-Indole Annulated Heterocycles via a Formal Thio [3 + 3]-Cyclization. *Org. Lett.* **2015**, *17*, 42. (b) Jiang, X.-X.; Sun, Y.-L.; Yao, J.; Cao, Y.-M.; Kai, M.; He, N.;

Zhang, X.-Y.; Wang, Y.-Q.; Wang, R. Core Scaffold-Inspired Concise Synthesis of Chiral Spirooxindole-Pyranopyrimidines with Broad-Spectrum Anticancer Potency. *Adv. Synth. Catal.* **2012**, *354*, 917.

(19) Liang, J.-Y.; Shen, S.-J.; Chai, X.-Q.; Lv T. Lewis-Base-Catalyzed [1 + 2 + 2] Annulation Reaction of Morita–Baylis–Hillman Carbonates with Unsaturated Pyrazolones: Construction of All-Stereogenic Carbon Cyclopentane-Fused Dispiropyrazolones. *J. Org. Chem.* **2018**, *83*, 12744.

(20) Garden, S. J.; Guimarães, C. R. W.; Corréa, M. B.; Oliveira, C. A. F. D.; Pinto, A. D. C.; Bicca de Alencastro, R. Synthetic and Theoretical Studies on the Reduction of Electron Withdrawing Group Conjugated Olefins Using the Hantzsch 1, 4-Dihydropyridine Ester. *J. Org. Chem.* **2003**, *68*, 8815.